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Applied organometallics: Cp*Co(III)-catalysed C-H functionalisation as a maturing tool for the synthesis of heterocyclic compounds

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ABSTRACT

Heterocycle compounds are prevalent throughout the natural world and therefore it is unsurprising that they have become a key component in many pharmaceutically relevant molecules. Unfortunately, synthetic methods for their preparation are often complicated and exhibit poor sustainability. In order to develop more efficient and sustainable routes to the synthesis of these useful and valuable heterocyclic compounds chemists have started to develop new innovative approaches. One approach which has provided a number of successes in recent times are synthetic procedures operating through a key direct C-H bond functionalisation step. This chapter highlights the state-of-the-art for preparing a diverse range of heterocyclic compounds using a cobalt-catalysed C-H bond functionalisation approach, specifically applying Cp*Co(III)-type catalysts.

1. Introduction

1.1 Heterocycles and C-H functionalisation

Heterocyclic fragments are key features of many natural products including nucleic acids, pigments, vitamins and many medicinally active compounds, amongst others. It is therefore not surprising that compounds prepared in the laboratory containing heterocyclic fragments have been found to exhibit a range of biological properties, as well as other important uses. Indeed, inspection of pharmaceutical compounds approved by the United States Food and Drug Administration (FDA) over recent years, highlights the importance of small molecules compounds containing heterocyclic fragments.[1,2] However, synthetic approaches to the preparation of many of these heterocyclic compounds still remain highly challenging, in contrast to nature where these compounds can often readily made through well evolved metabolic processes. As a result, significant attention has recently been focused on designing new innovative routes for the preparation of a wide range of heterocycles using both established and new synthetic tools. Work focused on new synthetic routes often provides novel reactivities and greener, more sustainable approaches. In this context, direct C-H bond functionalisation utilising organometallic catalysts has become a very powerful tool, as a result of the highly reactive organometallic intermediates which arise. Much of this work has parallels to well established palladium-cross coupling chemistry (Figure 1.1a),[3-5] except it utilises more ubiquitous C-H bonds, rather than limiting pre-installed C-X (X = halide or triflate) groups, thus producing less waste and more opportunities (Figure 1.1b), although providing more challenges in the context of selectivity. Although palladium can be applied in catalytic C-H functionalisation procedures,[6,7] its rising cost and the desire to discover more diverse activities has led researchers to investigate other metals as replacement. As a result, first-row (3d)

transition metals are attracting a lot of attention,[8,9] due to their relative abundance, relative low cost and rich (redox) chemistries. One metal, namely cobalt, has provided numerous successes and a wide range of catalytic C-H functionalisation procedures have been reported to date, which have been well reviewed.[10-16] This chapter aims to provide an overview of the recent literature concerning the use of cobalt-catalysed direct C-H bond functionalisation for the preparation of a wide range of heterocyclic compounds, specifically based on the Cp*Co(III)-type catalysts. On the way we will discuss intriguing features of the mechanisms in order to lay the foundations for future researchers to rationally design new synthetic procedures.

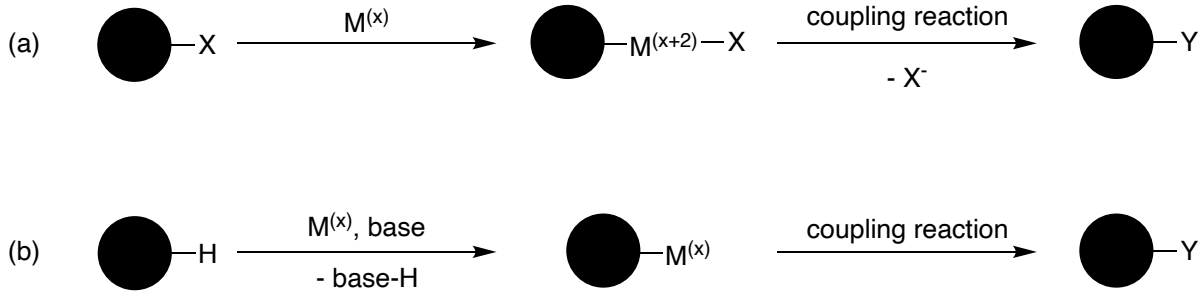
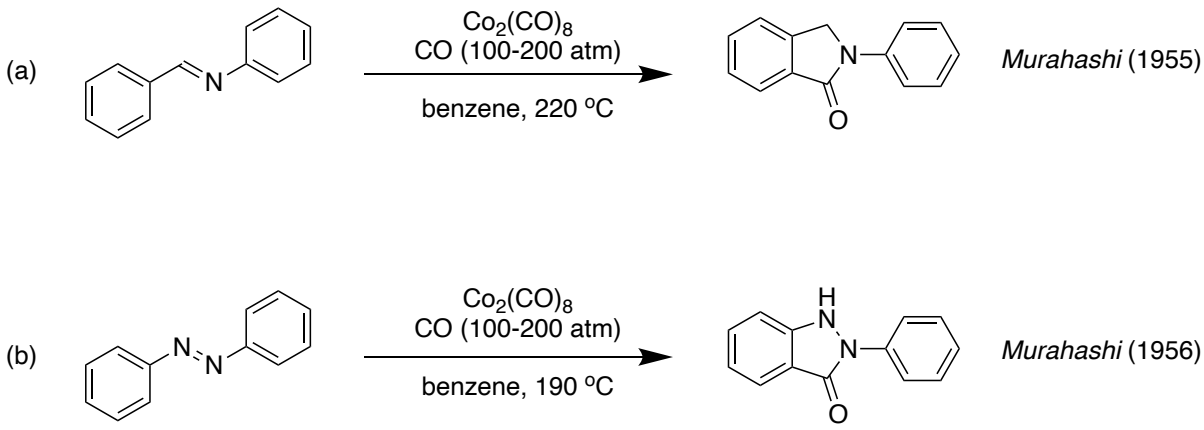


Figure 1.1 Differences between traditional cross-coupling and more modern C-H bond functionalisation approaches: *(a) Generic traditional cross-coupling reaction. (b) Generic direct C-H bond functionalisation reaction. M = metal, X = halide/triflate, Y = installed functionality.*

1.2 Cobalt-catalysed C-H functionalisation; a brief historical overview

The intention of this chapter is to provide an overview of the applicability of Cp*Co(III)-type catalysts in heterocycle formation. However, a brief overview of the developments in this field is very important in understanding how the field has come to its current fruition.

Cobalt-catalysed C-H functionalisation has long been known. Indeed, as early as 1955 Murahashi reported on the cobalt-catalysed couplings of carbon monoxide to aldimines and azobenzenes to realise isoindolinones and indazolones, respectively (Scheme 1.1),[17,18] which both occurred through a formal C-H bond functionalisation. The catalyst in this example was low-valent $Co_2(CO)_8$ and despite the reaction been long reported, the mechanism remains unclear, although one could propose that the initial C-H activation operates through a directed oxidative addition across the C-H bond resulting in a higher valent organometallic intermediate.

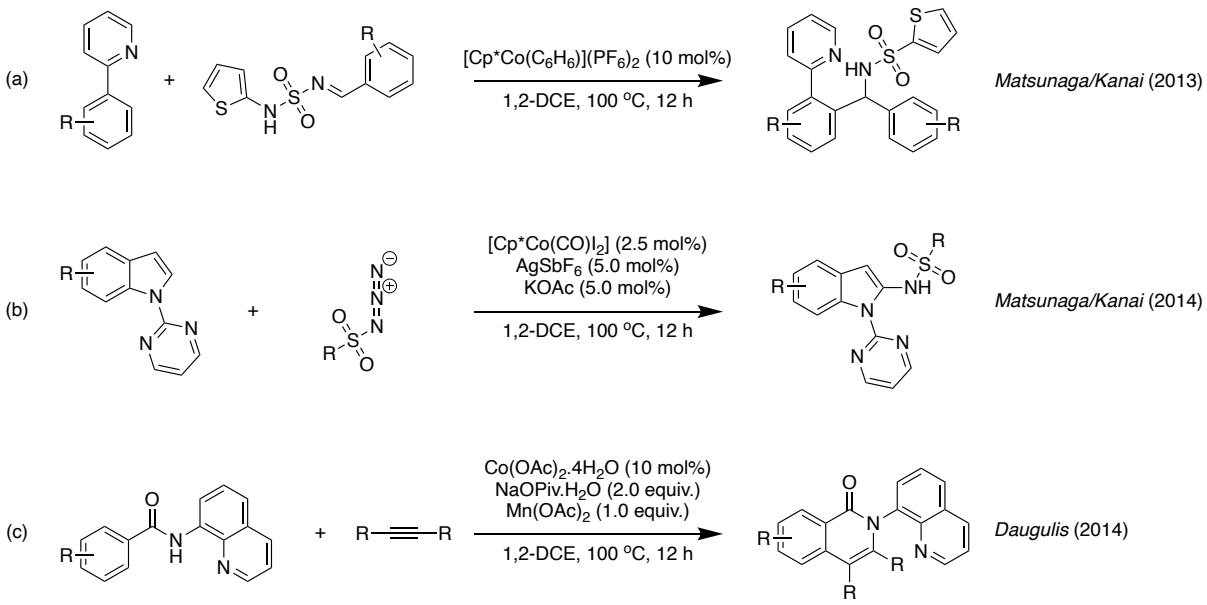


Scheme 1.1 Early examples of heterocycle formation through cobalt-catalysed C-H activation using the low-valent approach.

After this initial disclosure, surprisingly relatively little work was carried out in the field apart from notable contributions from Kochi (1973), who reported that benzene could be coupled with trifuoroacetic acid through a cobalt-catalysed C-H activation, operating through a Single Electron Transfer (SET) mechanism.[19] Later in 1994, Kisch showed that aromatic azo compounds could be ortho-alkylated using Co(I) catalysts. Again, after this report, the field returned to relative dormancy, until 2010 when Yoshikai instigated what can be considered a revolution in the application of cobalt-catalysed C-H functionalisation.[20] In this work the authors showed it possible to couple

aryl pyridines to alkynes in a linear type coupling. This was a breakthrough as the low-valent cobalt species required for the oxidative addition across the C-H bond was formed in-situ through reaction of readily available $CoBr_2$ and Grignard reagents, being stabilised by the inclusion of a phosphine. After this seminal work, many groups followed this low-valent approach to cobalt-catalysed C-H bond functionalisation and numerous reports detail its successful application.[21]

The big break-through in the corresponding high-valent approach came only as recently as 2013/14 when almost simultaneously, Daugulis and Matsunaga/Kanai both reported high-valent cobalt-catalysed C-H functionalisation protocols, albeit with completely differing approaches (Scheme 1.2).[22] The work from Matsunaga/Kanai focused on the use of Cp*Co(III)-type catalysts (initially $[Cp^*Co(C_6H_6)](PF_6)_2$ before moving towards the now more utilised $[Cp^*Co(CO)I_2]$ catalyst; Scheme 1.2a and b), analogous to the rhodium complexes introduced by Miura in 2007.[23] This initial work with these Cp*Co(III) catalysts focused on what can be classified as linear additions, but as will be discussed further in this chapter, the application to the synthesis of heterocycles soon became the focus of much and successful attention. Meanwhile, Daugulis employed the use of the previously known 8-aminoquinoline directing group (Scheme 1.2c),[24] which many studies have suggested stabilises the cobalt(III) species which is responsible for the C-H activation step.[25] This work from Daugulis is also of particular interest to this chapter as it provided facile access to heterocyclic compounds starting from cheap catalysts and substrates.



Scheme 1.2 Seminal work on the high-valent approach to cobalt-catalysed C-H functionalisation.

1.3 Direct annulative *vs*. cascade approaches to heterocycle formation using direct C-H bond functionalisation

Given the presence of so many C-H bonds in most molecules and the desire to develop robust, highly selective procedures, the use of a chelating "directing group" is indispensable. In linear C-H functionalisation procedures, the directing group is normally removed at the end of the procedure, whereas, procedures forming heterocycles usually include part, or all, of the initial directing group in the resulting heterocyclic compound. Figure 1.2 shows the two general routes towards the formation of heterocycles using metal-catalysed C-H functionalisation. The annulative approach is particularly common and usually results from a reductive elimination of the metal when it is coordinated to both the directing group and the newly installed functionality, furnishing the heterocyclic compound. Typically, the installed functionality arises from the migratory insertion of an unsaturated compound across the initially formed organometallic species. In contrast, the cascade approach involves

the installation of the new functional group through C-H bond functionalisation, which is followed by removal of the metal from both the directing group and the new functionality (usually by proto-demetallation). Thereafter, the directing group and new functionality react to form the heterocyclic compound in many cases without the addition of any other reagents. The advantage of the latter approach is that this may operate in a redox neutral process, thus not requiring the addition of stoichiometric oxidant to regenerate the active catalyst (this will be exemplified and highlighted later in this chapter).

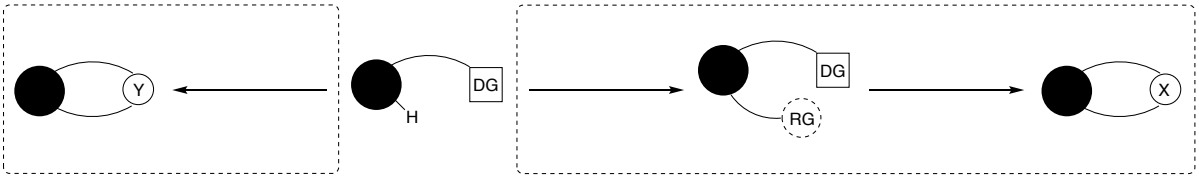


Figure 1.2 Different approaches to heterocycle formation; DG = directing group, RG = reactive group, X and Y = newly formed linker in the heterocycle.

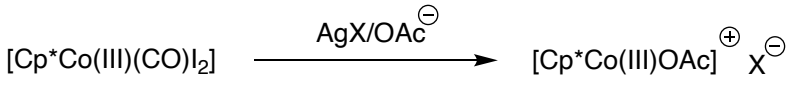
1.4 Redox neutral and redox active mechanisms

Finally, before highlighting the many examples of heterocycle synthesis utilising Cp*Co(III) C-H bond functionalisation catalysis, it is necessary to briefly discuss and introduce the potential redox nature of the catalytic procedures.

When using high-valent cobalt in C-H bond functionalisation, it has been found that it is actually the Co(III) species which performs the C-H bond activation step and elegant studies by Ribas have clearly shown this to be the case using their model macrocyclic system.[25] Therefore, one of the key advantages of using the Cp*Co(III) approach over the cheaper Co(II) salts is that the catalyst is actually in its active oxidation state at the start of the procedure, thus obviating the necessity for an external oxidant to convert

the Co(II) salt to the active Co(III) species. Generally, the use of Co(II) salts is common as there are very few sources of Co(III) salts available, with $Co(acac)_3$ being a limited example (acac = acetylacetonate), but bearing strongly coordinated ligands, which impede catalyst coordination to substrates and coupling partners.

When applying the Cp*Co(III)-type catalysts, as a result, the need for an oxidant only occurs if there is either a reductive elimination step or β-H elimination in the mechanism. Indeed, many protocols using Cp*Co(III) catalysts are redox neutral as they take advantage of proto-demetallation steps (resulting in highly sustainable catalytic protocols). During this chapter we will clearly indicate the redox nature of the reactions and also highlight from where the oxidant is derived; besides external oxidants, the oxidant may be part of the substrate itself in the form of an innovative approach using an “oxidising bond”. As a final note, the Cp*Co(III) catalysts are generally considered to form the reactive catalyst species in-situ; the stable 18-electron $[Cp^*Co(III)(CO)I_2]$ reacts with a silver salt in the presence of a base to form the actual cationic catalyst species (Scheme 1.3).



*Scheme 1.3 Generation of catalytically active cationic species for Cp*Co(III)-catalysed C-H functionalisation protocols.*

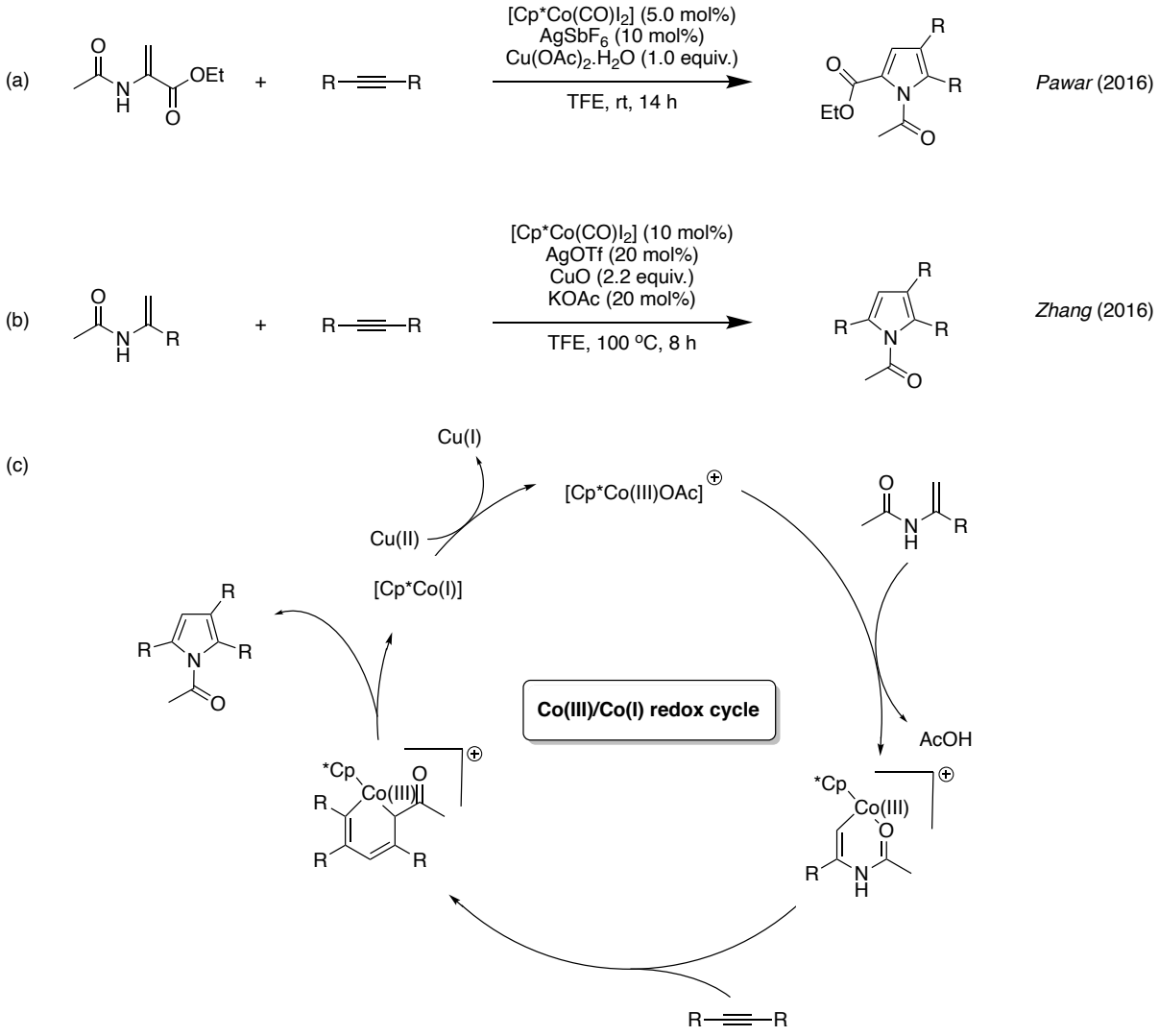
2 Cp*Co(III)-catalysed synthesis of heterocyclic compounds

The following sections provide examples of the synthesis of a wide variety of heterocyclic compounds using the Cp*Co(III) catalysts. General reaction conditions and mechanistic insights will be provided in order to fully highlight each individual approach.

2.1 Examples of five-membered heterocycle synthesis

2.1.1 Pyrroles

Pyrroles are important structural building-blocks and are well exploited throughout the chemical sciences. This demand means that the search for novel and facile approaches to the synthesis of pyrrole derivatives is of significant interest. In 2016, both Pawar and Zhang reported on annulative approaches for preparation of pyrrole derivatives starting from readily available enamines (Scheme 1.4).[26,27] Of note, is the fact that the procedure reported by Pawar operates at room temperature, although if the reaction occurs at elevated temperature the 'deprotected' *N*-H pyrroles are obtained through reaction with the silver salt, thus obviating the necessity for a separate deprotection step. Both of the protocols are proposed to operate through a Co(III)/Co(I) mechanism, arising from the inclusion of a reductive elimination step, where copper is used to re-oxidise the eliminated Co(I) to the active Co(III) catalyst state (Scheme 1.4c). This redox-active mechanism is very typical for a significant number of annulation-type reactions with alkynes as coupling partners involving Cp*Co(III) catalysts.



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185 *Scheme 1.4 (a and b) Synthesis of pyrroles from readily available enamines and*
186 *alkynes through an oxidative annulation. (c) Proposed redox-active Co(III)/Co(I)*
187 *mechanism for the protocol.*

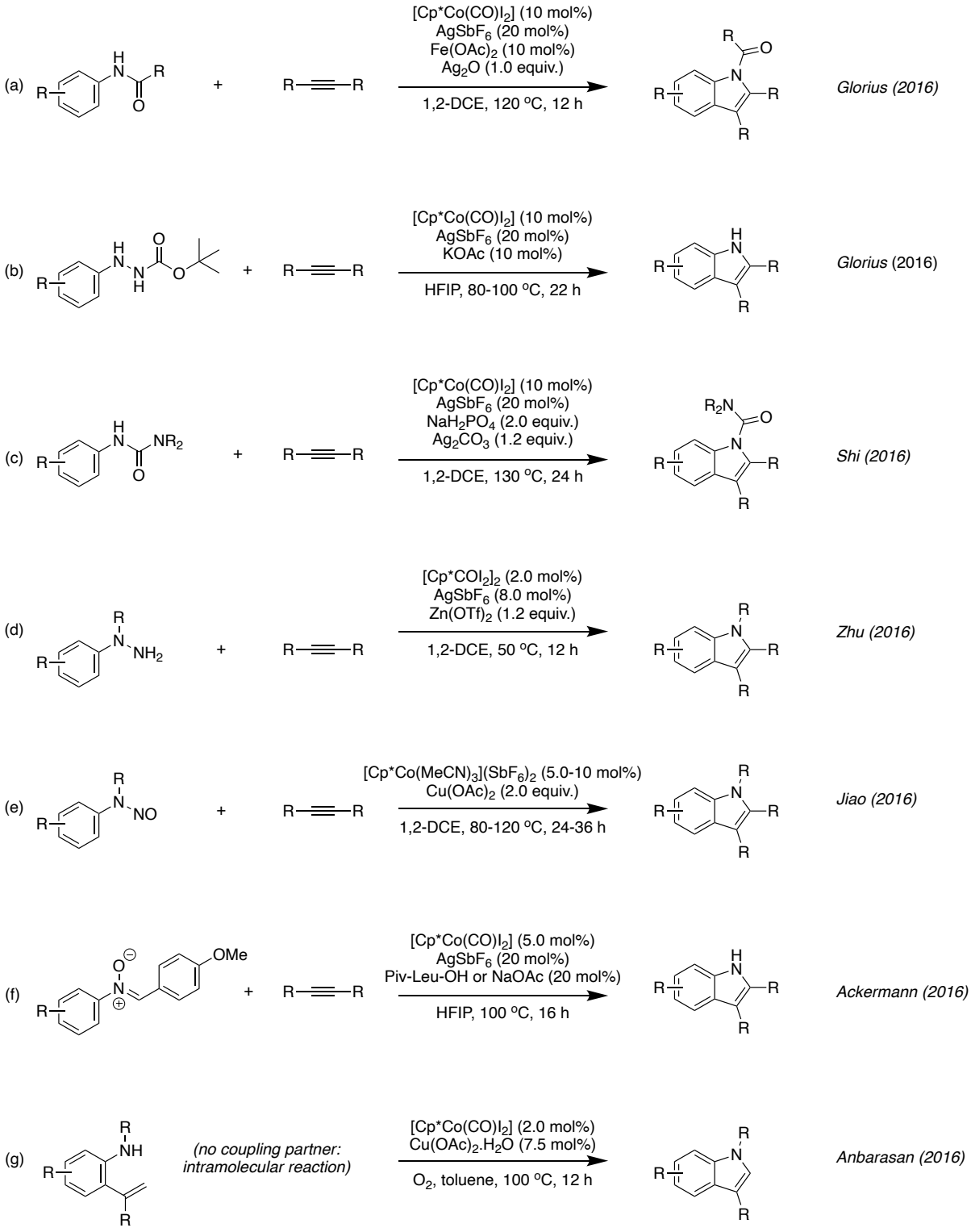
188 **2.1.2 Indoles**

189 Catalytic procedures for the synthesis of indoles have been particularly well studied
190 through Cp*Co(III)-catalysed C-H bond functionalisation approaches. Scheme 1.5
191 highlights different procedures that have been applied. Despite the similarity of these
192 protocols, there appears to be a significant amount of mechanistic diversity after
193 considering the proposed mechanisms. In the seminal work of Glorius in 2016,[28] a

reductive elimination results in a Co(III)/Co(I) mechanism with Ag_2O acting as the terminal oxidant. The same authors thereafter reported a different approach, albeit still based on the original Co(III)/Co(I) mechanism; installation of a Boc group provided what can be described as an "oxidising directing group".[29] In this case, the Co(I) species resulting from the reductive elimination completes an oxidative addition across the N-Boc bond furnishing the Cp*Co(III) catalytically competent species. Subsequent work by Shi was proposed to follow the Co(III)/Co(I) mechanism, employing Ag_2CO_3 as terminal oxidant in a similar approach to the original work of Glorius.[30] Meanwhile, Zhou provided access to indoles starting from arylhydrazines but provided limited insight into the mechanism apart from to suggest that the alkyne transiently forms the allene which is the species which inserts in the migratory insertion step.[31]

In contrast to the redox-active examples, Jiao proposed that after alkyne insertion, an intramolecular substitution reaction occurs to form the C-N bond and break the N-N bond.[32] However, this is only a proposal and by inspection in this case, the "oxidising directing group" events cannot be ruled out. Later in the same year, Ackermann reported on the use of nitrone compounds as the basis for a protocol for the preparation of indoles.[33] In this example the authors propose that after migratory insertion of the alkyne, N-O bond cleavage occurs with C-O bond formation. The resulting Co(III) enolate then regenerates the catalytically competent catalyst through proto-demetallation, before the protected ortho-amino ketone hydrolyses and finally through intramolecular condensation the indole product is formed. In a final example of indole synthesis, Anbarasan utilised a novel and innovative intramolecular approach.[34] This protocol is unusual with cobalt as it uses a secondary amine group to direct the C-H activation step. The protocol is proposed to operate through a Co(III)/Co(I) mechanism using copper as the terminal oxidant, which itself is re-

oxidised by oxygen, meaning that advantageously the terminal oxidant is also only required in catalytic amounts.

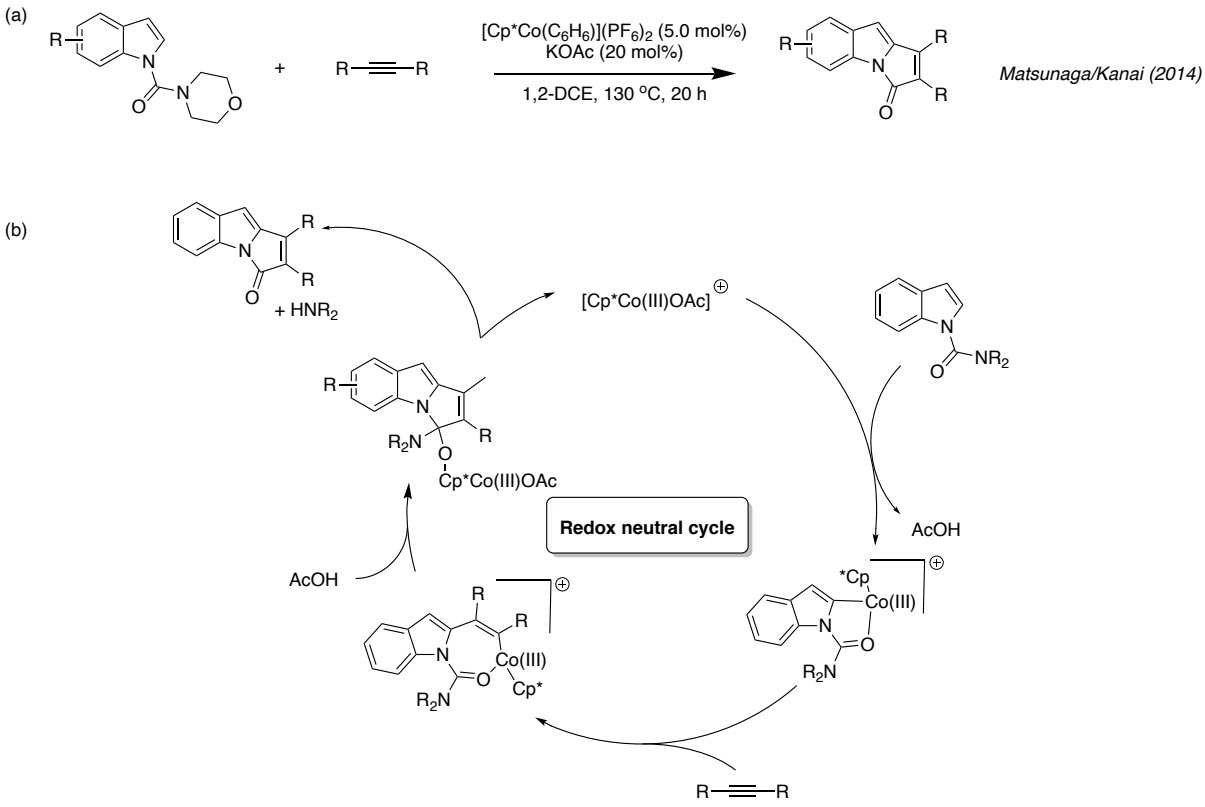


*Scheme 1.5 Synthesis of indoles by different approaches using Cp*Co(III)-catalysts.*

2.1.3 Pyrroloindolones

The preparation of pyrroloindolones was one of the seminal works for the preparation of heterocycles using Cp*Co(III) catalysts. In 2014, Matsunaga and Kanai presented a comprehensive study on the coupling of N-carbamoyl indole bearing a morpholine unit with alkynes.[35] The authors studied the mechanism through a Density Functional Theory (DFT) study and proposed a redox neutral mechanism (Scheme 1.6a). This protocol is of particular interest as it demonstrates that the Cp*Co(III) catalyst is more reactive than the corresponding Cp*Rh(III) variant. This observation was proposed to be due to the nucleophilicity of the organocobalt species. The detailed computational analysis of the Cp*Co(III) C-H activation step highlighted two important points: (a) the CMD step occurs via the expected 6-membered transition state, with the alternative 4-membered transition state being significantly higher in energy, and (b) the high spin triplet pathway is energetically accessible, with only $\Delta\Delta G = 0.4$ kcal mol^{-1} in favour of the singlet pathway. In 2017, the same authors expanded the computational study to understand the proceeding alkenylation *vs*. annulation reactions.[36] As was originally proposed the reaction occurs by alkyne insertion into the Co-C bond, forming the important 7-membered cobaltocycle intermediate. This is the divergent point in the mechanism, with alkylation occurring via proton transfer from the coordinated AcOH to the alkenyl carbon and the annulation via a C-C ring closing step prior to AcOH coordination (Scheme 1.6b), and subsequent protonation of the amide nitrogen. The authors noted that the experimentally observed product of the reaction is dependent on the nature of the amide group; with morpholine preferring annulations while dimethlyamide preferring undergoing alkenylation. This is accounted by the small energy differences ($\Delta\Delta G < 2$ kcal mol^{-1}) between the competing transition states. A third reaction pathway is also possible, *via* a directing-group migration and subsequent

protonation of the indole nitrogen, forming a tetrasubstituted alkene product, which has been experimentally realised. Once again, the high spin triplet states were shown to energetically accessible (and for some intermediates/transition states favoured) throughout all mechanisms.

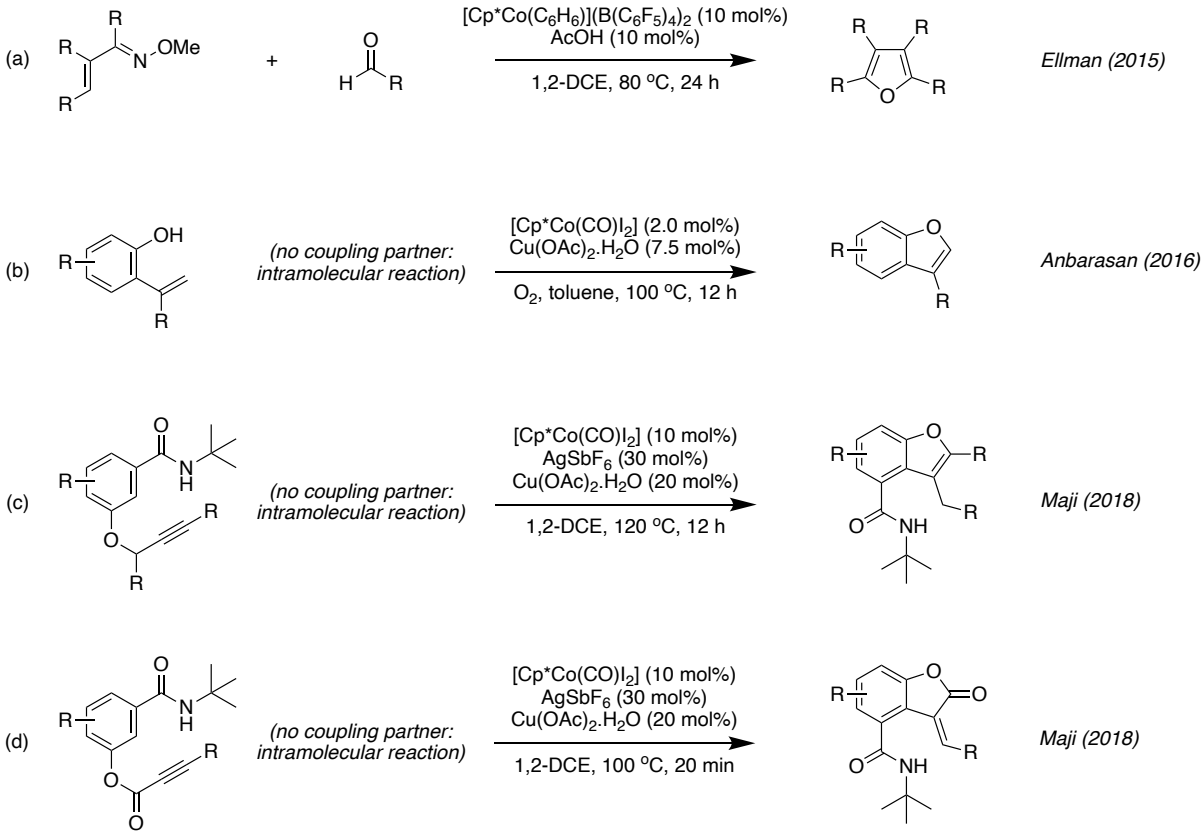


*Scheme 1.6 (a) Synthesis of pyrroloindolones through Cp*Co(III) catalysis. (b) Proposed redox neutral mechanism for the protocol.*

2.1.4 Furans, benzofurans and benzofuranones

Furan and furanone motifs are prevalent in a wide range of biological molecules. In the context of Cp*Co(III) catalysis, surprisingly, relatively few approaches have been developed for their preparation. The group of Ellman, in 2015, provided the first example of multi-substituted furan synthesis from readily available α,β-unsaturated oximes and aldehydes (Scheme 1.7a).[37] In this case, as there is no addition of terminal oxidant and therefore the reaction is likely to be redox neutral and passes through a

cascade approach with furan motif forming through cyclative capture using a hydroxyl nucleophile. In a completely different approach, Anbarasan extended the previously mentioned intramolecular coupling approach for indole synthesis towards ortho-alkenylphenols to realise benzofurans (Scheme 1.7b).[34] Again this is protocol is proposed to operate through a Co(III)/Co(I) redox mechanism, with the phenol directing the C-H activation step and then forming part of the heterocycle as a result of the reductive elimination. Finally, a procedure for the preparation of both benzofurans and benzofuranones was disclosed in 2018 by Maji (Scheme 1.7c).[38] This method utilised a tethered alkyne which inserts across the cobaltacycle formed after C-H activation. Once migratory insertion has occurred, a proto-demetallation step takes place, leading to the benzofuran or benzofuranone. The operative mechanism is as a result redox neutral, providing a very efficient and appealing route towards the target compounds, with the amide directing group remaining intact at the end of the procedure, providing opportunity for a second C-H functionalisation to be applied, as the authors further demonstrated.

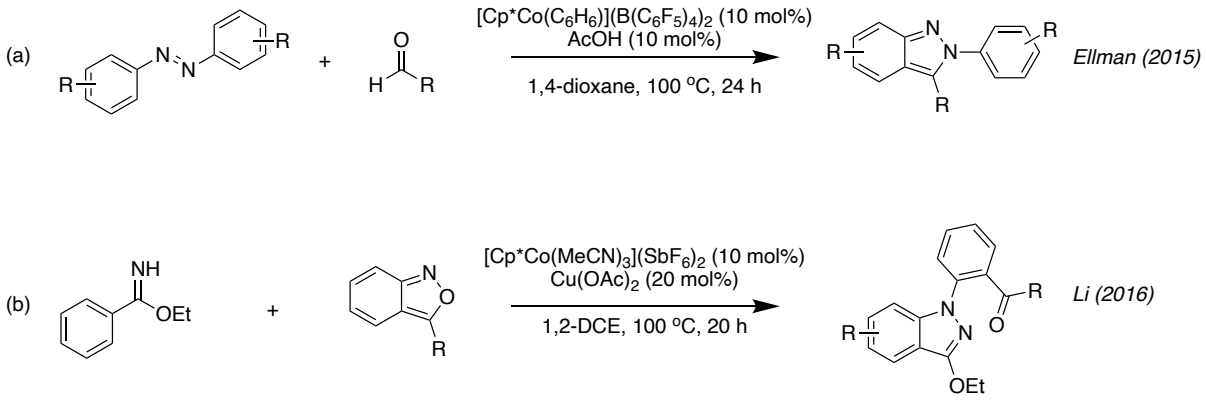


*Scheme 1.7 Cp*Co(III)-catalysed protocols for the preparation of furan and furanone derivatives*

2.1.5 Indazoles

In addition to the multi-substituted furan synthesis reported by Ellman, the same work also described the functionalisation of azobenzenes with aldehydes to furnish 2*H*-indazoles (Scheme 1.8a).[37] This mechanism also operates through a redox neutral process, in a cascade approach with the off-cycle step being a cyclative capture with a hydroxyl leaving group. Contrasting 1*H*-indazoles have also been prepared through a Cp*Co(III) approach. In 2016, Li demonstrated that through the coupling of imidates and anthranils, that 1*H*-indazoles could be readily prepared (Scheme 1.8b).[39] The mechanism is proposed to operate through initial coordination and C-H activation of the imidate substrate, before the anthranil coordinates and resultantly forms a nitrene intermediate. Thereafter, the nitrene inserts across the Co-aryl bond, followed by a

proto-demetallation, meaning that overall the mechanism is redox neutral. In order to form the final heterocycle, a copper-catalysed Single Electron Transfer (SET) mechanism is proposed.

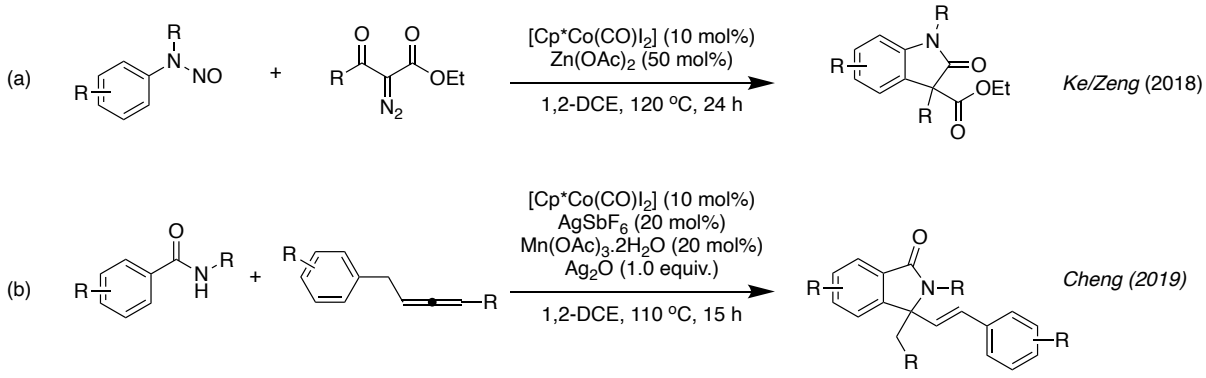


*Scheme 1.8 Indazole synthesis by two different approaches obtained by Cp*Co(III) catalysis.*

2.1.6 Oxindoles

Substituted oxindoles have been prepared using α-diazo-β-ketoesters as coupling partners with *N*-nitrosoanilines (Scheme 1.9a).[40] The mechanism, which was studied by DFT, involves an unusual Wolff rearrangement of the cobalt carbenoid intermediate which then inserts across the Co-aryl bond, although the authors were unable to rule out direct Wolff rearrangement of the α-diazo-β-ketoesters into the ketene under the reaction conditions. Overall, the mechanism is redox neutral as there is no reductive elimination to form the heterocyclic product, as it is proposed to occur through a direct cyclative pathway after the migratory insertion step, resulting in the release of HNO after the proto-demetallation. More recently, Cheng provided access to a different isomer through the coupling of readily available benzamides with allenes (Scheme 1.9b).[41] This example was shown to have a β-hydride elimination step after the initial migratory insertion of the allene. This step is followed by insertion of the alkene into

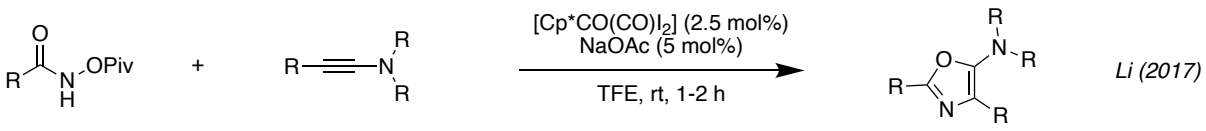
the resulting cobalt-hydride, before a final reductive elimination forming the desired product meaning that the mechanism is Co(III)/Co(I) redox active.



*Scheme 1.9 Cp*Co(III)-catalysed protocols for the preparation of oxindoles.*

2.1.7 Oxazoles

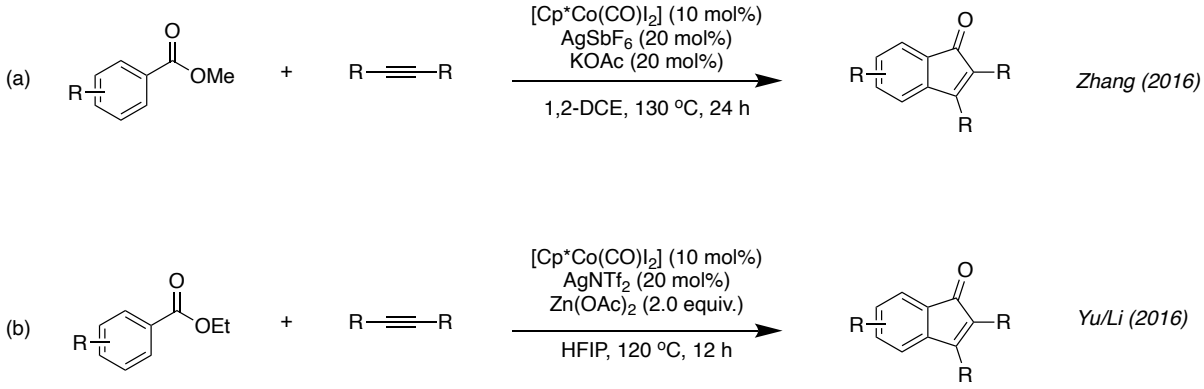
Cp*Co(III)-catalysed coupling of N-(pivaloyloxy)amides with ynamides forming a range of substituted important 5-aminooxazoles was reported by Li in 2017 (Scheme 1.10).[42] The authors propose that there is no formal C-H activation step in this procedure, which marks this example as unique in this chapter. Initially, the Cp*Co(III) catalyst coordinates to a deprotonated amide and O-atom of the pivaloyl group. Thereafter, the ynamide converts to the keteniminium ion coordinates to the cobalt, before 6-*exo-trig* cyclisation generates an organometallic cobaltacyclic intermediate. At this point it is not clear how the final product is formed as several pathways are possible, resulting that this work provides opportunities for others to study and elucidate the unusual mechanism in the future.



*Scheme 1.10 Unique mild Cp*Co(III)-catalysed protocol for the preparation of oxazoles.*

2.1.8 Indenones

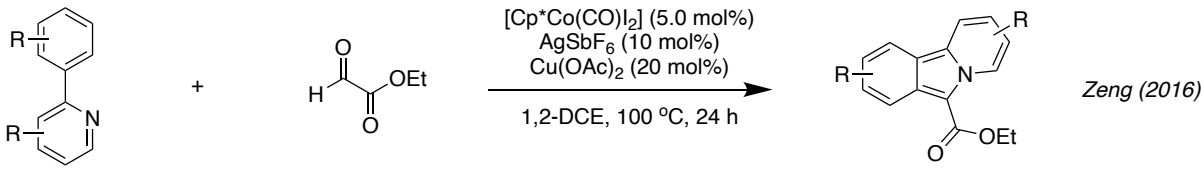
Both the groups of Zhang and Yu/Li simultaneously reported on a procedure for the preparation of indenones from benzoates and alkynes (Scheme 1.11).[43,44] Both reports propose that the C-H activation is directed by the carbonyl of the ester functionality, before a migratory insertion of the alkyne and subsequent reaction with the ester to form a cyclic species, followed by elimination of cobalt furnishing the indanone. As such, the mechanism is redox neutral, with Zhang[43] providing MALDI-TOF evidence of the organometallic migratory insertion intermediate.



*Scheme 1.11 Indenones preparation from benzoates through Cp*Co(III) catalysis.*

2.1.9 Indolizines

A single example of indolizine preparation can be found, which was reported by Zeng in 2016 (Scheme 1.12).[45] This work provides a facile coupling of phenyl and alkenyl pyridines with predominantly ethyl oxoacetate, although limited examples with oxo-aryl-acetaldehyde and oxo-alkyl-acetaldehyde are included. The protocol is proposed to be redox neutral with nucleophilic attack of the pyridine on the formed hydroxyl functionality providing the heterocyclic product.



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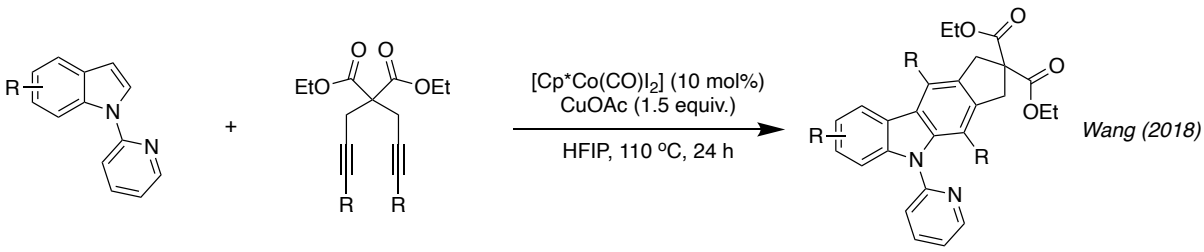
346 *Scheme 1.12 Cp*Co(III)-catalysed protocol for the preparation of indolizines.*

347 2.1.10 Carbazoles

348 A rare example of a double migratory insertion mechanism was reported by Wang in
349 2018,[46] utilising a diyne as coupling partner with benzindole as substrate (Scheme
350 1.13). The mechanism involves a first migratory insertion to the cobaltacycle, formed
351 after C-H activation, and then a second migratory insertion to a cobaltacycle arising
352 from a second C-H activation. Finally, reductive elimination provides the carbazole
353 product and the Cp*Co(I) species, resulting in this being a Co(III)/Co(I) redox active
354 protocol.



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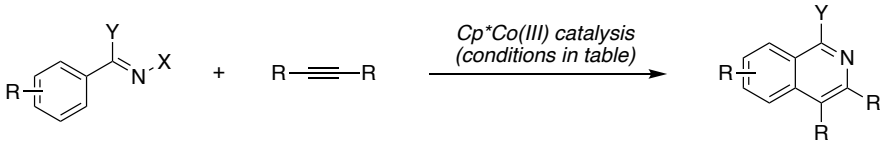
356 *Scheme 1.13 Protocol for the synthesis of highly complex carbazoles using*
357 *Cp*Co(III) catalysis.*

358 2.2 Examples of six-membered heterocycle synthesis

359 2.2.1 Isoquinolines

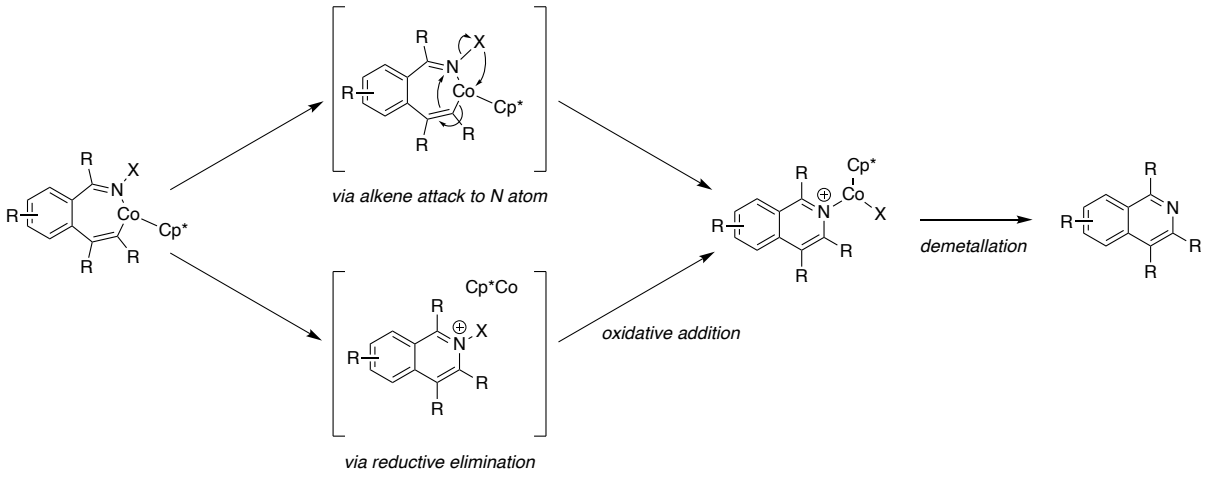
360 Isoquinolines have attracted a lot of attention, with many research groups reporting
361 efficient procedures for their synthesis using Cp*Co(III) catalysis. One of the most
362 popular routes is through the utilisation of oximes (Table 1.1).[47-55]

*Table 1.1 Cp*Co(III)-catalysed protocols for the synthesis of isoquinolines from oximes and alkynes.*



Entry	X	Y	Conditions	
1	OH	Alkyl or phenyl	[Cp*Co(III)(CO)I_2] (10 mol%) NaOAc (20 mol%) TFE, 80 °C, 24 h	*Sundararaju (2015)*[47]
2	OAc	Alkyl or phenyl	[Cp*Co(III)(CO)I_2] (10 mol%) $AgSbF_6$ (20 mol%) KOAc (20 mol%) 1,2-DCE, 80-120 °C, 24 h	*Kanai/Matsunaga (2015)*[48]
3	OAc	Alkyl	[Cp*Co(III)(CO)I_2] (10 mol%) $AgSbF_6$ (20 mol%) NaOAc (20 mol%) 1,2-DCE, 120 °C, 16 h	*Ackermann (2015)*[49]
4	OH	NHR (R= alkyl or phenyl)	[Cp*Co(III)(CO)I_2] (10 mol%) CsOAc (20 mol%) TFE, 120 °C, 24 h	*Cheng (2016)*[50]
5	H	Alkyl or phenyl	[Cp*Co(III)(CO)I_2] (10 mol%) AgOTf (20 mol%) $Ce(SO_4)_2$ (2.0 equiv.) KOAc (20 mol%) 3 Å MS, CH_3NO_2, 80 °C, 24 h	*Li/Wang (2016)*[51]
6	S(O)^{t}Bu	Phenyl	[Cp*Co(III)(CO)I_2] (10 mol%) $AgNTf_2$ (20 mol%) AcOH (1.0 equiv.) 1,2-DCE, 120 °C, 18 h	*Li (2016)*[52]
7	NHBoc	Alkyl	[Cp*Co(III)(CO)I_2] (10 mol%) $AgSbF_6$ (20 mol%) AcOH (20 mol%) HFIP, 100 °C, 30 min	*Zhu (2016)*[53]
8	NH_2	Alkyl or phenyl	[Cp*Co(III)(CO)I_2] (10 mol%) $AgSbF_6$ (20 mol%) PivOH (25 mol%) TFE, 120 °C, 14 h	*Pawar (2016)*[54]
9	H	Alkoxyl	[Cp*Co(III)(CO)I_2] (10 mol%) $AgNTf_2$ (20 mol%) AcOH (20 mol%) 1,2-DCE, 80 °C, 12 h	*Ding/Sun (2017)*[55]

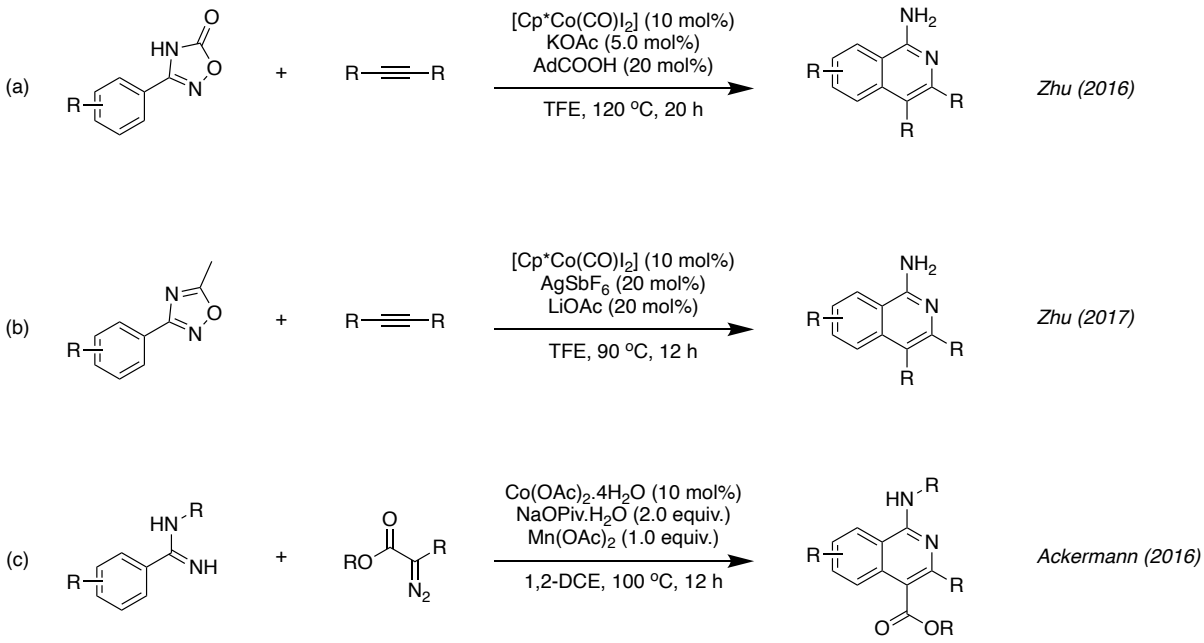
Although these protocols appear very similar, there appears to be significant mechanistic diversity. This diversity arises from the possibility from the migratory insertion intermediate to react in two distinct ways, albeit ending with the same product (Scheme 1.14); (a) intramolecular cyclisation through alkene attack of the *N*-atom or (b) a reductive elimination step. Upon inspection of the literature, there is no compelling evidence for either route to be more likely than the other and so this may be of interest for researchers looking to fully understand these potentially useful protocols.



*Scheme 1.14 Proposed mechanistic routes for the Cp*Co(III)-catalysed addition of alkynes to oximes. (a) redox neutral and (b) redox active. NB. if X = H the reaction can be assisted by an acetate anion.*

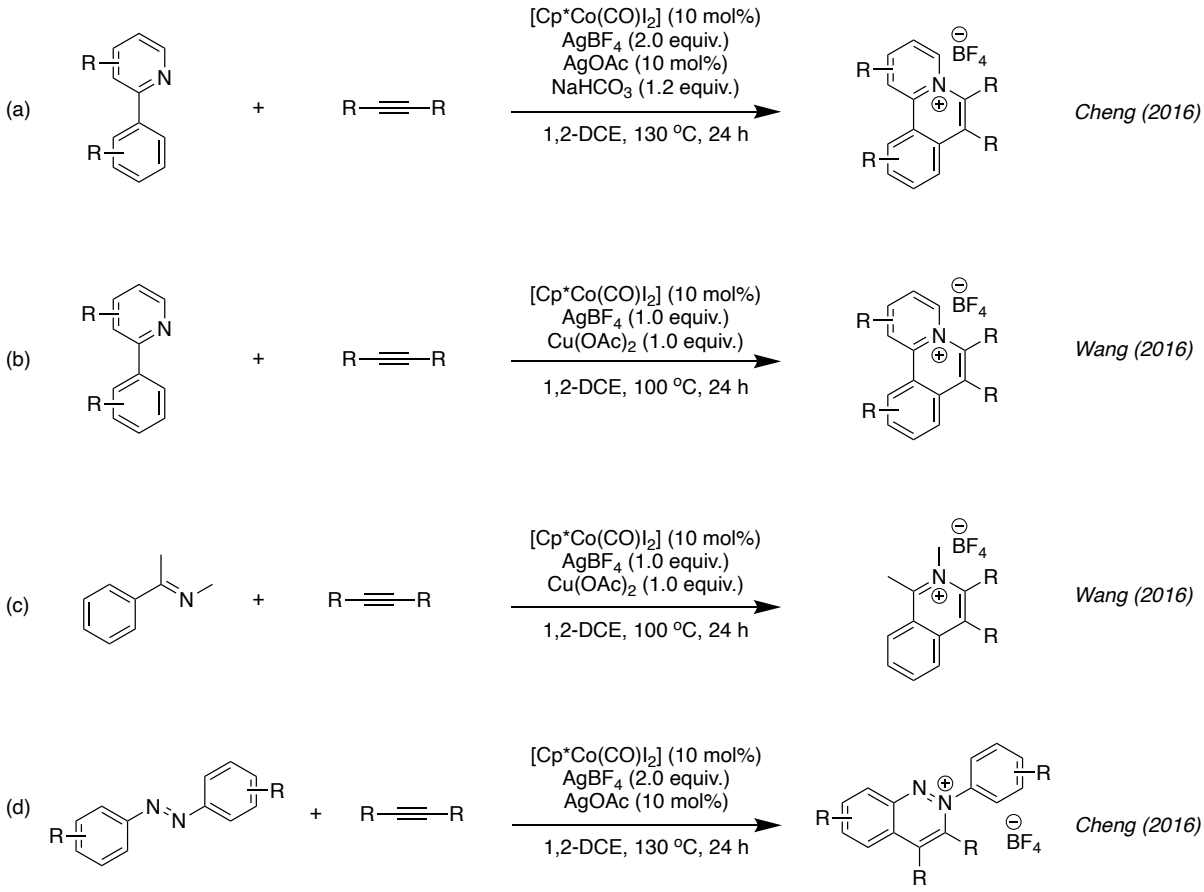
Other substrates have also been applied for the synthesis of isoquinolines (Scheme 1.15), although the reports from Zhu utilised oxadiazolones[56] and oxadiazoles,[57] which could be considered surrogates of the imidates shown in Table 1.1. One significantly different approach was that described by Ackermann, where highly-reactive diazo compounds were applied as coupling partners rather than alkynes (Scheme 1.15c).[58] In this mechanism, the cobalt-carbene intermediate leads to the migratory insertion of the carbene, before proto-demetallation furnishes the linear coupling product. This

intermediate then converts to the desired amino-isoquinoline through intramolecular nucleophilic attack of the amidine and subsequent β-elimination of water.



*Scheme 1.15 Alternative approaches to synthesis of isoquinolines using Cp*Co(III) catalysis*

A number of routes to isoquinoline salts have also been reported (Scheme 1.16) as these are also useful functional molecules.[59,60] Of particular interest is the work of Wang, who reported the use of both phenylpyridines and aryl imines to provide a variety of differently substituted isoquinoline salts in the same work.[60] The authors clearly indicate the likelihood of a reductive elimination step, resulting in a Co(III)/Co(I) redox mechanism. The migratory insertion step of this procedure has been studied in detail by Pérez-Temprano, where the work provides important X-ray crystal structures of the previously proposed intermediate species.[61] Finally, the same procedure is also applicable from the preparation of cinnolinium salts, providing access to a new family of heterocycles (Scheme 1.16c).[59]

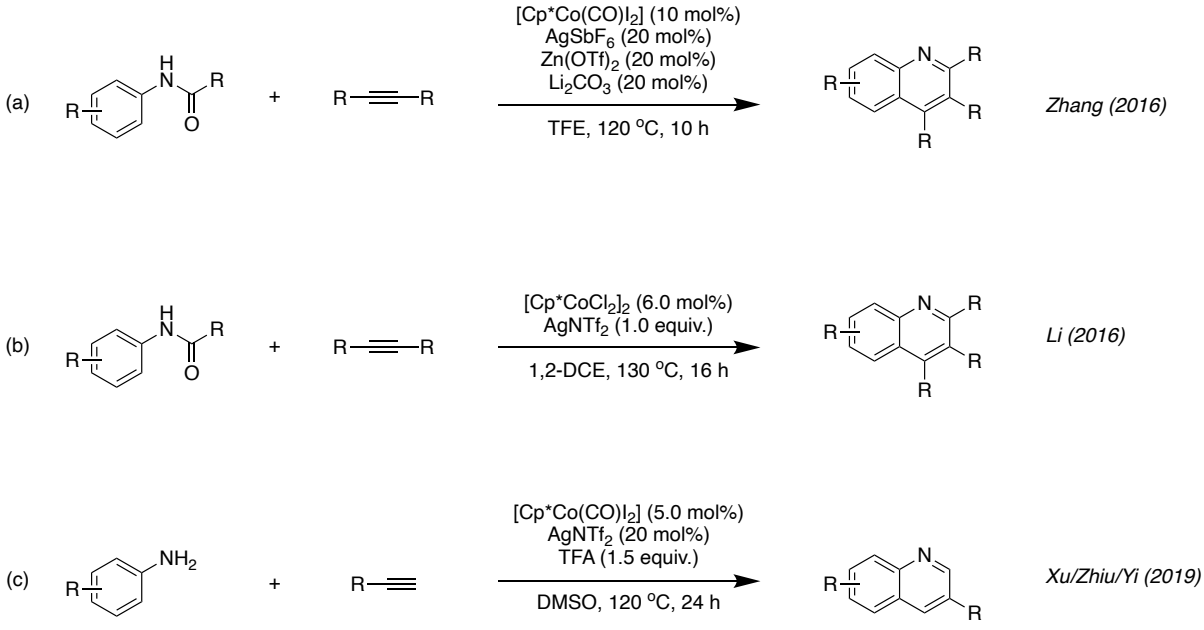


*Scheme 1.16 Preparation of isoquinoline salts through Cp*Co(III) catalysis.*

2.2.2 Quinolines

The preparation of quinolines through Cp*Co(III) redox neutral catalysis was first reported using anilides and alkynes independently by both Zhang and Li in 2016 (Scheme 1.17a and b).[62,63] In this work, the carbonyl of the anilide directs the C-H activation. Migratory insertion of the alkyne across the cobalt-aryl bond provides an intermediate, which then reacts through an intramolecular cyclisation to form a cyclic product, which proto-demetallates and dehydrates to from the desired quinoline. Recently, insightful studies on the intermediates of this mechanism have been reported by Pérez-Temprano, where again, key intermediates have been isolated and X-ray crystal structures obtained of the previously proposed cobaltacycle species.[64]

More recently in 2019, Xu/Zhiu/Yi provided a similar protocol starting from more readily available anilines (Scheme 1.17c).[65] This protocol uses alkynes and DMSO as coupling partners to form the quinoline product, with it being known the TFA activates DMSO. The coupling of in-situ formed $^{+}CH_2SMe$ cation to the aniline and elimination of HSMe provides an imine species which is the key species to forming the quinoline product. This latter protocol provides access to vastly differently substituted analogues compared to the aforementioned work by Zhang and Li.

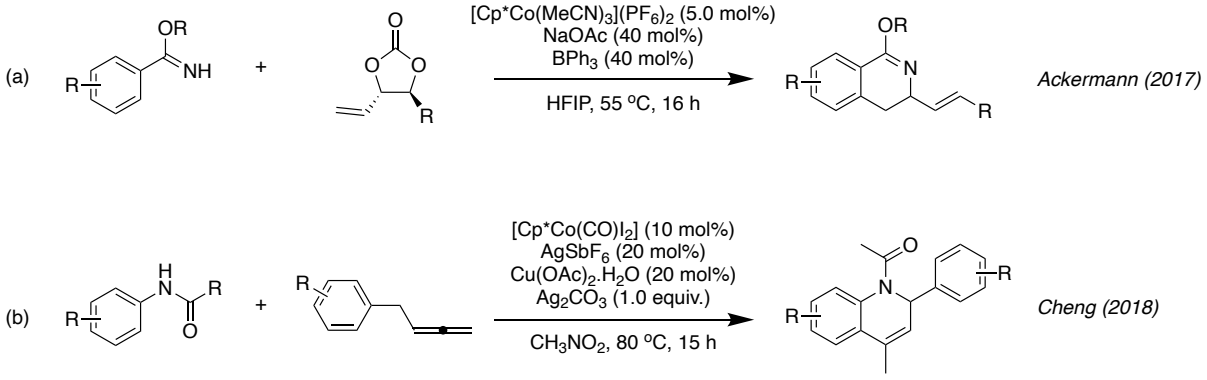


*Scheme 1.17 Use of anilides and anilines for the preparation of quinolines using Cp*Co(III) catalysis.*

2.2.3 Dihydroisoquinolines and dihydroquinolines

The partially reduced forms of both isoquinolines and quinolines, have both been prepared by Cp*Co(III) catalysis. In 2017, Ackermann reported on the allylation of imidates using vinyl carbonates (Scheme 1.18a).[66] The reaction mechanism is similar to that of alkynes with imidates to form isoquinolines (section 2.2.1; Table 1.1). The difference occurs in that after migratory insertion of the vinyl group, CO_2 extrusion

occurs, resulting in an unsaturated intermediate which provides a platform for intramolecular N-H allylation and elimination of a Cp*Co(III) species meaning that the mechanism is redox neutral. More recently, in 2018, Cheng provided a route towards dihydroquinolines from anilides and allenes (Scheme 1.18b).[67] The mechanism of this protocol is intriguing; the allene reacts with the cobalt-aryl through a migratory insertion step, resulting in an *exo*-cyclic alkene. Thereafter, Cp*Co(I) is released through a β-H elimination, which is re-oxidised to Cp*Co(III). This Cp*Co(III) species then facilitates the 1,4-addition of the N-H to the diene group, as a result furnishing the desired heterocycle.

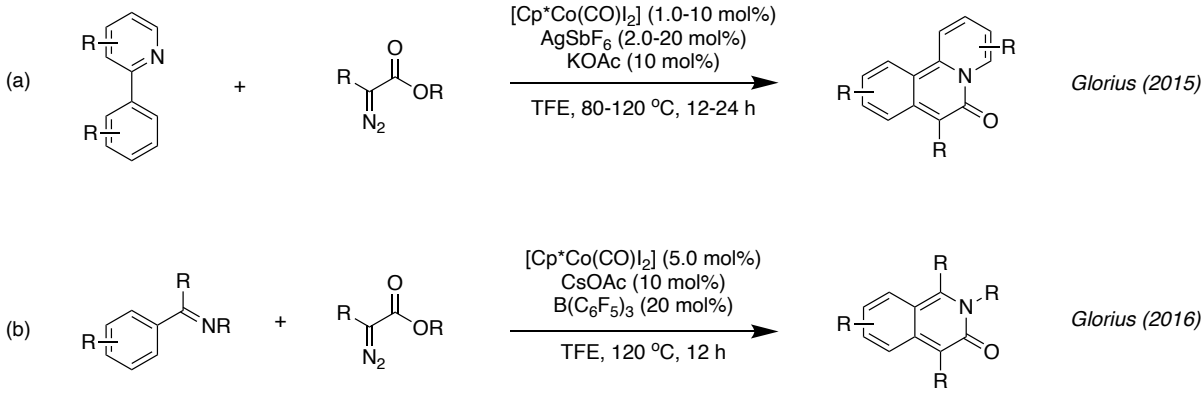


*Scheme 1.18 Cp*Co(III)-catalysed approaches for the preparation of dihydroisoquinolines and dihydroquinolines.*

2.2.4 Isoquinolones

In the context of isoquinolone synthesis, Cp*Co(III) catalysis takes two different approaches (Schemes 1.19 and 1.20); (a) coupling with diazo compounds, or (b) coupling with alkynes. In 2015, Glorius reported that phenylpyridines and diazo esters as coupling partners could be used to prepare isoquinolones using Cp*Co(III) (Scheme 1.19).[68] The mechanism was proposed to involve the generation of a metal carbenoid species, which through migratory insertion and proto-demetallation forms a

ketone intermediate. This ketone intermediate reacts with the pyridine through Lewis acid-assisted nucleophilic cyclisation and through loss of methanol, the final isoquinolone. Soon after, the same group reported on the use of alkyl imines in place of phenylpyridine substrates.[69] The proposed mechanism is identical to the first report, although a catalytic amount of $B(C_6F_5)_3$ was added to promote the C-H activation and metal-carbene formation.



*Scheme 1.19 Use of diazo compounds in for the preparation of isoquinolones through Cp*Co(III) catalysis.*

Extensive DFT mechanistic studies by Cramer and Qu elucidated the mechanism for the phenylpyridine and diazo ester reaction (Scheme 1.19a)[70] confirming the proposed mechanism. The calculations suggest, for the Cp*Co(III) catalyst, the C-H activation step is reversible, and the metal-carbene formation (with N_2 extrusion) being rate determining. Due to the small energy differences between the concerted and stepwise pathways for the Rate Determining Step (RDS), the authors suggest both processes may be operative. Additionally the study provided mechanistic insight into comparison of Cp*Co(III) vs Cp*Rh(III), highlighting the effect of the increased Lewis acidity of the Co catalyst. For the Co(III) system various spin states were calculated, however unlike the Pyrroloindolones (Section 2.1.3) only the singlet surface was shown to be energetically accessible. The role of the 2,2,2-trifluoroethanol solvent was explored,

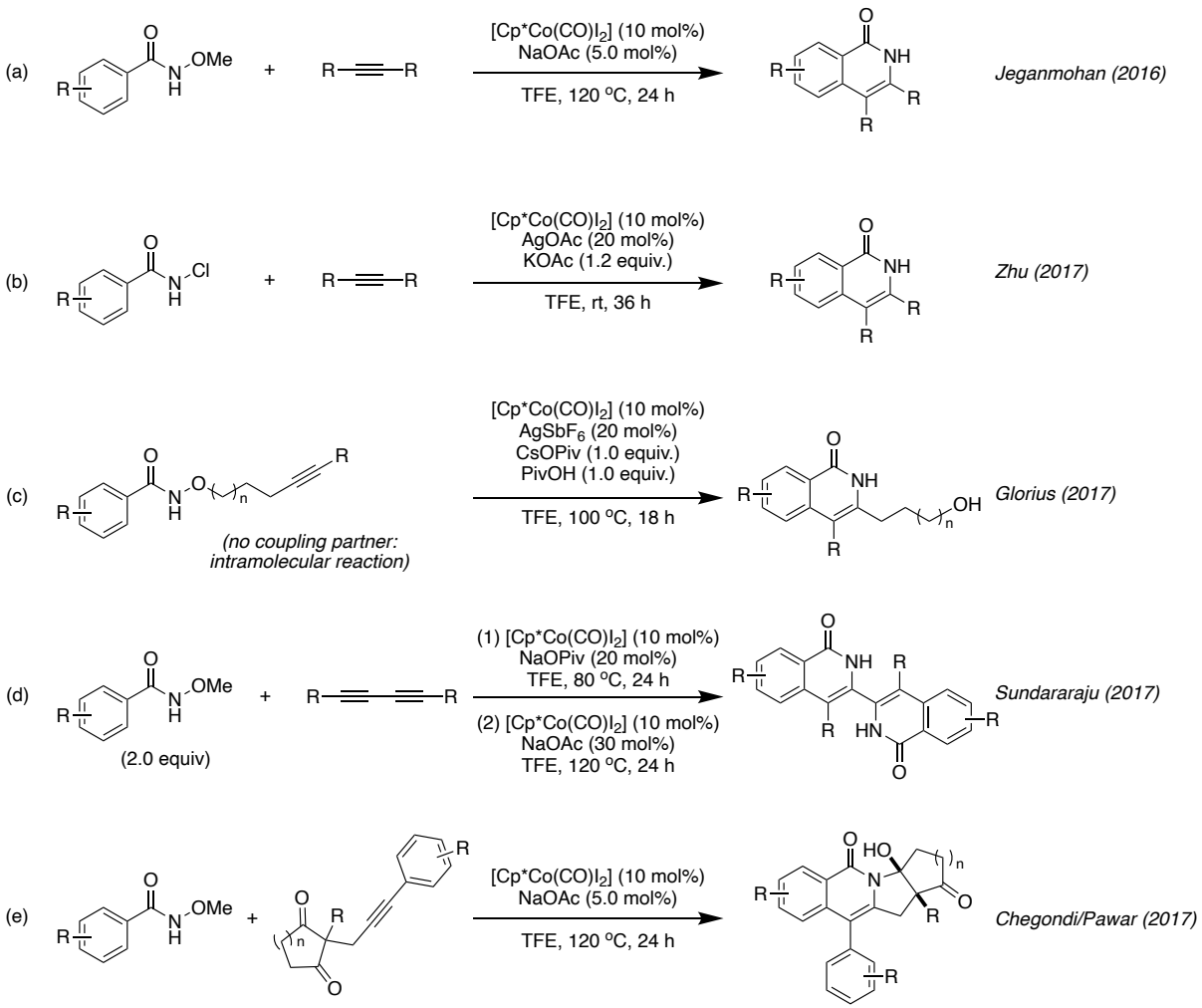
using a mixed implicit-explicit solvent model, highlighting the solvent assisted concerted methanol elimination process occurring for both the Co and Rh mechanisms. Thus, suggesting that further tuning of the acidity of the reaction medium may accelerate the reaction.

The reaction to form isoquinolones (Scheme 1.19b), has also been the subject of extensive DFT calculations, this time by Huang and Chen.[71] As discussed, Glorius had shown that addition of catalytic amounts of $B(C_6F_5)_3$ dramatically accelerates the reaction rates. The theoretical calculations suggests the $B(C_6F_5)_3$ additive facilitates the formation of the active catalytic species [Cp*Co(III)$(OAc)_2$] though coordination to an AcO^- ligand. Calculations also explored both the directing group C-H and N-H activation pathways; highlighting for Cp*Co(III), the preference for N-coordination-driven C-H activation over N-deprotonation directed C-H activation, in contrast to the equivalent Rh(III) system. The formation of the isoquinolone heterocycle was shown to occur *via* a nucleophilic addition reaction step, followed by a proton transfer to release the product and regenerate the catalyst. The energy span for the calculated mechanism was in excellent agreement with the observed experimental rate data.

In the context of alkyne coupling routes to form isoquinolones, benzamides are the substrate of choice (Scheme 1.20). All the examples of this approach take advantage of the presence of an "oxidising directing group". This route was first reported by Jeganmohan in 2016 (Scheme 1.20a);[72] the work utilised the N-OMe group, where upon reductive elimination of the cobalt to form a Cp*Co(I) species and the heterocycle, the N-O bond was used to re-oxidise the cobalt to the catalytically competent Cp*Co(III). In a related example, Zhu utilised the N-Cl group, which is proposed to operate through a different mechanism (Scheme 1.20b).[73] The mechanism proposed suggests that in this case, C-H activation occurs, forming the

cobaltacycle intermediate, which is then oxidised form Co(III) to Co(V) as a result of the high oxidising reactivity of the N-Cl bond. Migratory insertion of the alkyne and reductive elimination furnish the isoquinolone product and competent Cp*Co(III). These two contrasting examples are intriguing as it demonstrates that small changes in the nature of the directing group can provide access to either Co(III)/Co(I) or Co(III)/Co(V) mechanistic manifolds. Finally, it should be noted that in this work the authors were also able to prepare, isolate and characterise the cobaltacycle intermediate, additionally showing that it is catalytically competent.

Taking advantage of N-OR type directing groups on amides, Glorius, Sundararaju and Chegondi/Pawar developed protocols for the synthesis of differently substituted isoquinolones (Scheme 1.20c-e).[74-76] Glorius, utilised an intramolecular approach, whereby the re-oxidation of the Cp*Co(I) across the N-O bond results in the liberation of the terminal alcohol.[74] Whilst, Sundararaju developed a facile route towards *bis*-isoquinolones[75] and Chegondi/Pawar provided an example of the preparation of highly complex isoquinolone derivatives using alkynediones as coupling partners.[76]



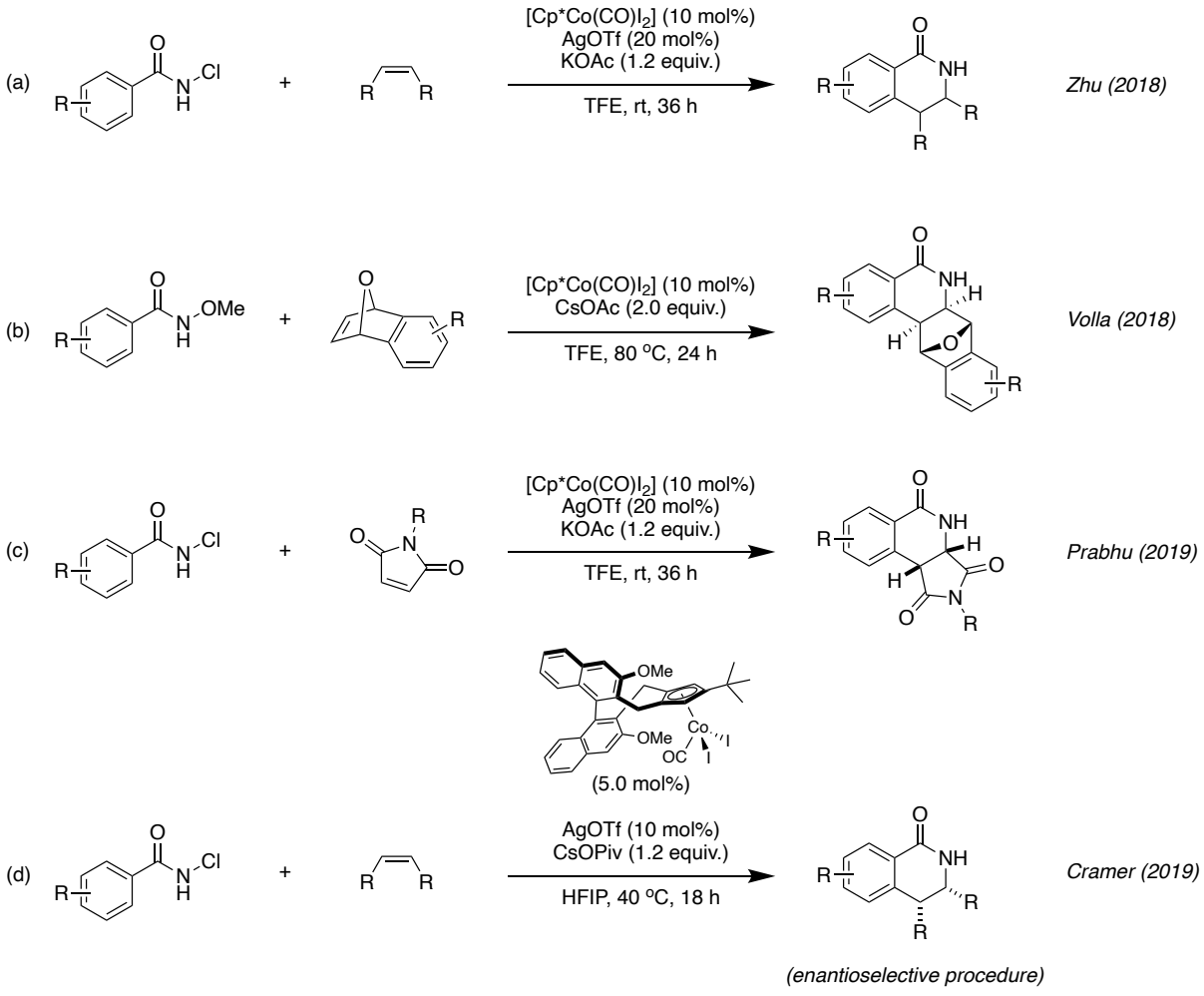
507

508 *Scheme 1.20 (a and b) Different approaches to the synthesis of isoquinolones using*
509 *benzamides and Cp*Co(III) catalysis. (c-e) Application of these approaches for the*
510 *synthesis of more complex compounds.*

511 **2.2.5 Dihydroisoquinolones**

512 The previous approach with coupling of alkynes to benzamides with "oxidising
513 directing groups" has been further transferred to olefin-based coupling partners
514 (Scheme 1.21), which has allowed protocols for preparation of a range of
515 dihydroisoquinolones of varying complexity.[77-80] The biggest and most exciting break-
516 through in this work is the recent report by Cramer,[80] which utilises a chiral $Cp^xCo(III)$
517 catalyst to provide access to dihydroisoquinolones with high enantio- and regio-purity

(Scheme 1.21d; Cp^x is a chiral Cp-based ligand). The authors studied a range of $Cp^xCo(III)$ catalysts with different chiral substitution on the chiral Cp^x ring, also finding that the enantioselectivities with $Cp^xCo(III)$ catalysts were much higher than those with analogous $Cp^xRh(III)$ catalysts. This enantioselective approach is likely to provide inspiration for a lot of future work and has already been contextualised by a review on the subject by Yoshino/Matsunaga.[81]

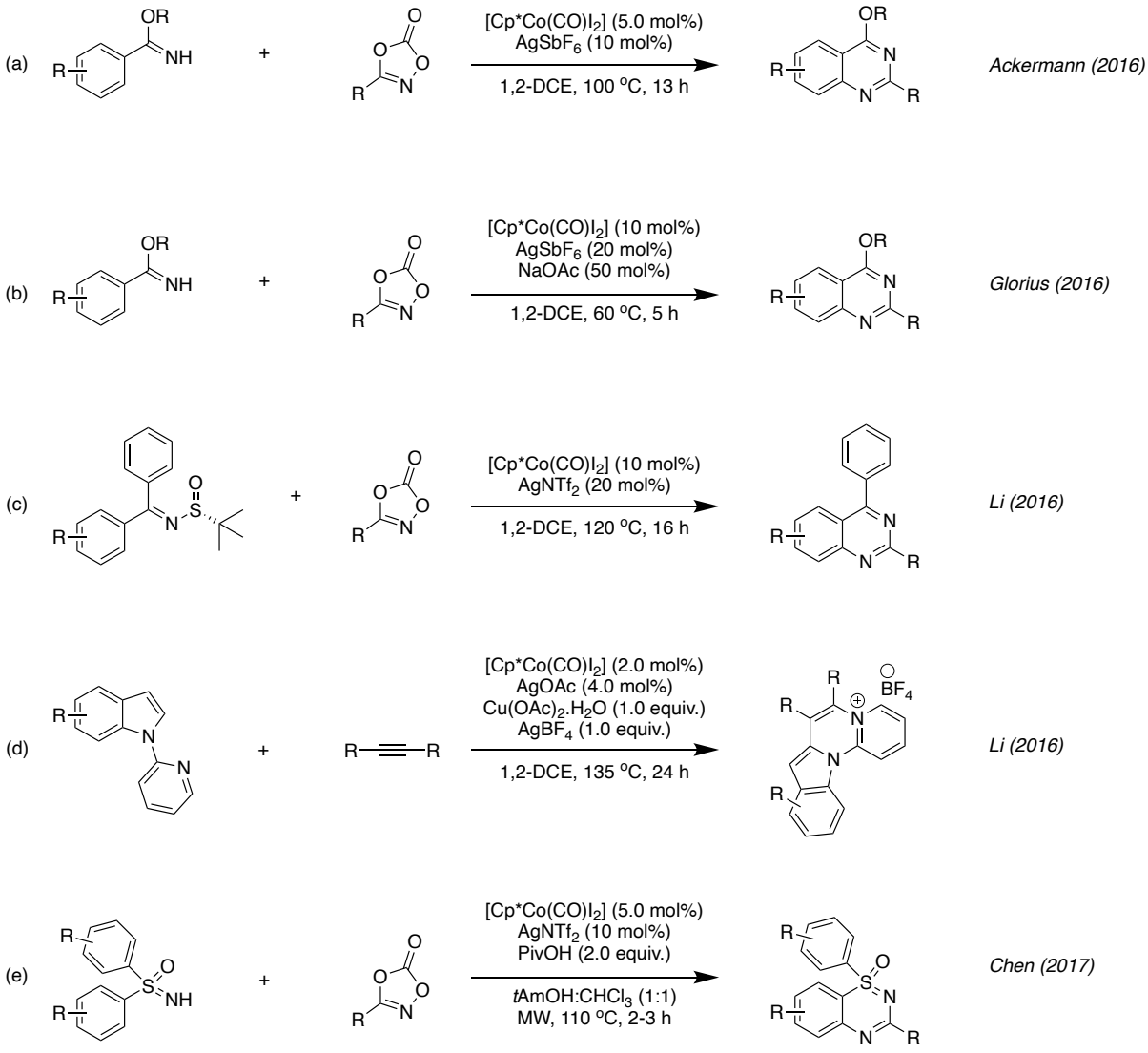


*Scheme 1.21 Synthesis of dihydroisolquinolones using Cp*Co(III) catalysis and benzamide derivatives.*

2.2.6 Quinazolines

Quinazolines have predominantly been formed under Cp*Co(III) catalysis by the coupling of imidates with dioxazolones as coupling partners (Scheme 1.22a-c). Initial work by Ackermann[82] and Glorius[83] provided access to alkoxy-substituted quinazolines, before later work by Li used *N*-sulfinylimines as a route towards access phenyl-substituted quinazolines.[84] All these examples operate through a redox-neutral cascade approach, with the final heterocycle forming step being the condensation between the intact imidate directing group and the installed amide functional group. In a slightly different approach Li reported on a procedure for the preparation of compounds which can be considered similar to quinazolines salts (Scheme 1.22d).[85] This example used benzoindoles and alkynes and involves a reductive elimination after the migratory insertion of the alkyne, implying a Co(III)/Co(I) mechanism. The reductive elimination generates a bond between the N-atom of the pyridyl directing group and the alkyne, resulting in a salt. The important intermediates of this mechanism were isolated and studied by Pérez-Temprano in seminal studies on Cp*Co(III)-catalysed annulation reactions.[86]

In a further extension of the early work by Ackermann and Glorius, a microwave-assisted protocol for the coupling of N*H*-sulfoximines with dioxazolones was reported by Chen (Scheme 1.22c).[87] This work provided facile access to related thiadiazine-1-oxides through the same cascade approach as for the quinazolines.

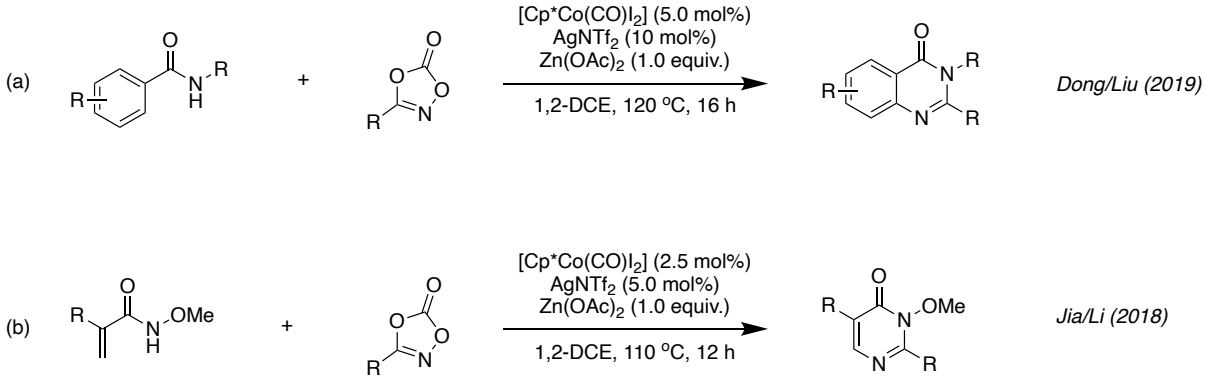


547

548 *Scheme 1.22 Different approaches for accessing quinazolines through Cp*Co(III)*
549 *catalysis.*

550 **2.2.7 Quinazolinones and pyrimidones**

551 Reaction of benzamides and acrylamides with Cp*Co(III) and dioxazolones has
552 provided efficient routes for the synthesis of quinazolinones and pyrimidines (Scheme
553 1.23).[88,89] Both of these routes operate by a redox neutral cascade approach, with
554 intramolecular dehydration occurring between the amide directing group and the
555 original amide directing group. This approach is very similar to the aforementioned
556 work for the synthesis of quinazolines from imidates.

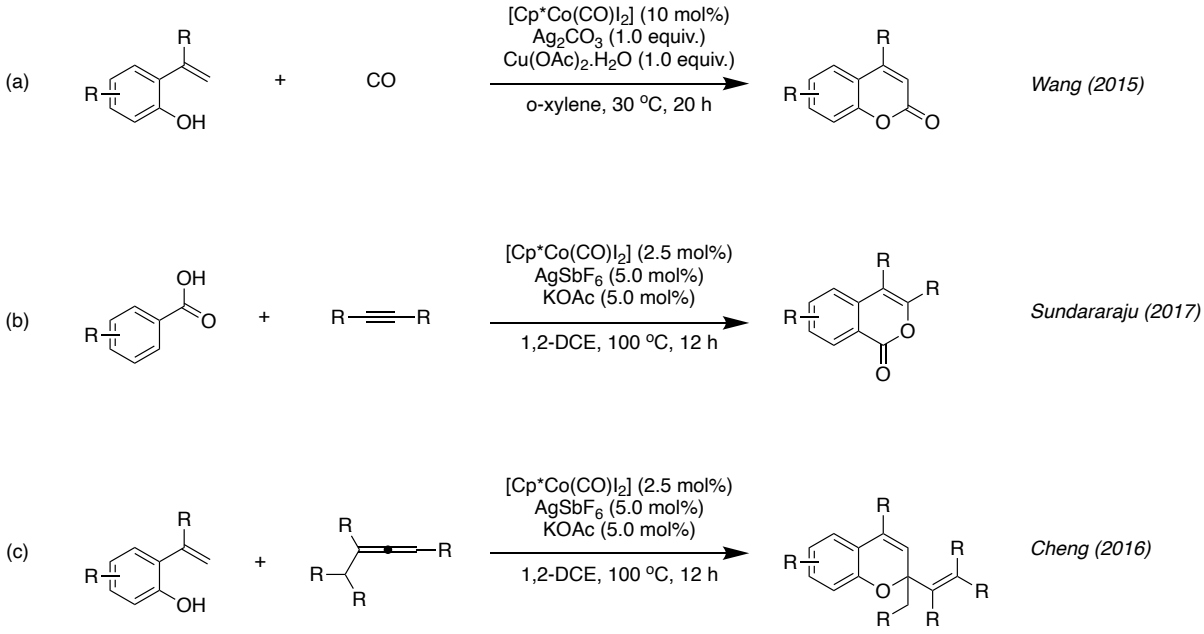


*Scheme 1.23 Preparation of quinazolinones and pyrimidines using Cp*Co(III) catalysis.*

2.2.8 Coumarins and chromenes

Procedures for the synthesis of two different isomers of coumarins have been reported by Wang and Sundararaju through distinctly different approaches (Scheme 1.24a and b).[90,91] Wang presented the coupling of alkenylphenols with carbon monoxide (Scheme 1.24a). This is an unusual coupling partner when using Cp*Co(III) catalysis, whereas examples have been presented previously using $Co(OAc)_2$ and the 8-aminoquinoline directing group approach. The mechanism proposes phenol directed C-H functionalisation of the alkene, followed by migratory insertion of carbon monoxide. Finally, reductive elimination provides the coumarin product, resulting in a Co(III)/Co(I) redox cycle utilising either Cu(II) or Ag(I) as the terminal oxidant to regenerate the catalytically competent Cp*Co(III) species. Meanwhile, for the other isomer, Sundararaju was able to attain C-H functionalisation directed by the acid group of benzoic acid (Scheme 1.24b). Migratory insertion of the alkyne, followed by reductive elimination provided the coumarin product, resulting in a Co(III)/Co(I) redox cycle.

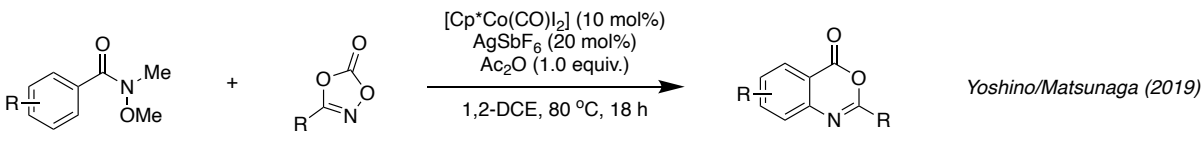
In 2016, Cheng provided a procedure for the formation of 2*H*-chromenes from alkenylphenols and allenes (Scheme 1.24c).[92] This work uses a similar approach to the Wang procedure for synthesis of coumarins except applying a different coupling partner. As such, the mechanism is remarkably similar, involving migratory insertion of the coupling partner, before a reductive elimination of the heterocyclic product, resulting in a Co(III)/Co(I) redox active procedure using Ag(I) as the terminal oxidant.



*Scheme 1.24 Cp*Co(III)-catalysed access to coumarins and chromenes.*

2.2.9 Benzoxazinones

Recently, Yoshino/Matsunaga have disclosed a procedure for the coupling of Weinreb amides and dioxazolones under Cp*Co(III) catalysis (Scheme 1.25).[93] Through addition of Ac_2O the authors were able to smoothly provide an interesting route towards benzoxazinones. This work is of interest due to the ability to provide heterocycles similar to quinazolinones.



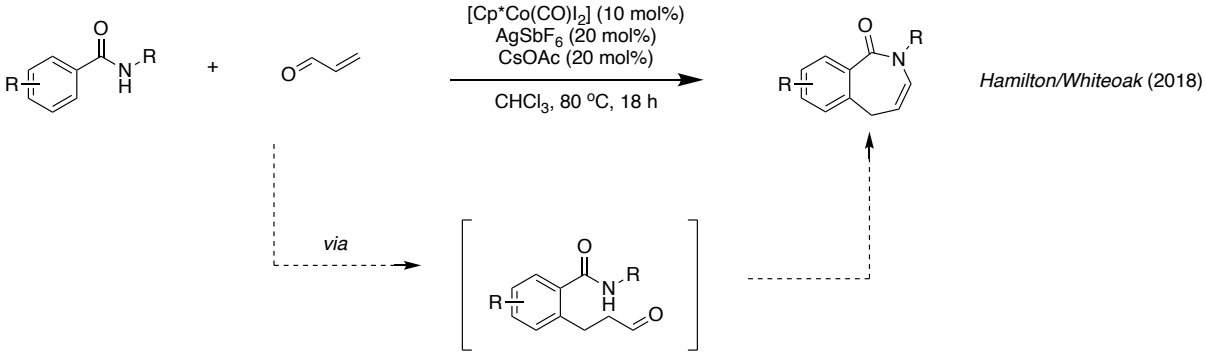
590 *Scheme 1.25 Use of Weinreb amides for the Cp*Co(III)-catalysed synthesis of*

591 *benzoxazinones.*

592 **2.3 Examples of seven-membered heterocycle synthesis**

593 **2.3.1 Azepinones**

594 In 2018 Hamilton/Whiteoak disclosed an efficient procedure for the synthesis of
595 azepinone compounds (Scheme 1.26).[94] This work was interesting in that the only by-
596 product was water, therefore providing a procedure with high atom economy and
597 sustainability. The authors performed a full DFT study on the linear coupling of α,β-
598 unsaturated ketones and fully explained why the linear coupling product was an
599 aliphatic ketone and not the corresponding α,β-unsaturated ketone formed by
600 traditional Heck-type coupling. The mechanism was found to be redox neutral, as a
601 result of the proto-demetallation after the migratory insertion of the olefin, rather than
602 β-hydride elimination which results in the not-detected α,β-unsaturated ketone
603 product. The authors then proposed that the azepinone was formed through the
604 intramolecular dehydration of the amide directing group of the substrate and the newly
605 coupled aldehyde.



606

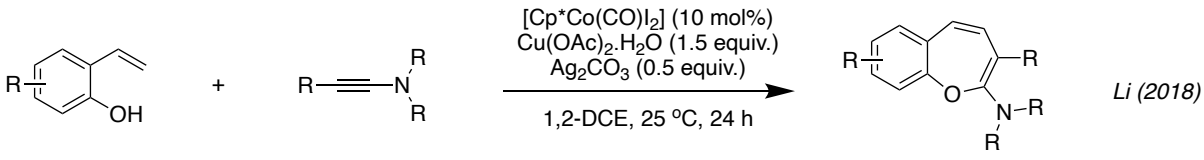
607 *Scheme 1.26 Facile synthesis of azepinones through the Cp*Co(III)-catalysed*

608 *coupling of benzamides with acrolein.*

The DFT calculations highlighted, and explained, a number is interesting observations. The nature of the benzamide ligand binding mode (O- vs N-coordination) was shown to be controlled by the electronic nature of the amide group. With O-coordination being preferable with the electron donating isopropyl group used in this study. This mode of coordination has been recently confirmed in a structural isolation study by Pérez-Temprano.[64] Comparison of the α,β-unsaturated ketone *vs* α,β-unsaturated ester reaction pathways highlighted an intriguing mechanistic divergence point whereby a "keto/enol" like isomerisation directs the reaction towards the respective alkylation or alkenylation products.

2.3.1 Benzoxepines

Seven-membered 2-aminobenzoxepines have been prepared through the Cp*Co(III)-catalysed coupling of alkenylphenols and ynamides (Scheme 1.27).[95] The mechanism is proposed to operate through phenol-directed C-H activation of the vinyl group, followed by migratory insertion of the alkyne moiety, from which the cobalt reductively eliminates to form the heterocyclic product. As a result of this reductive elimination step, the mechanism is redox-active, Co(III)/Co(I), with either Cu(II) or Ag(I) acting as the terminal oxidant.

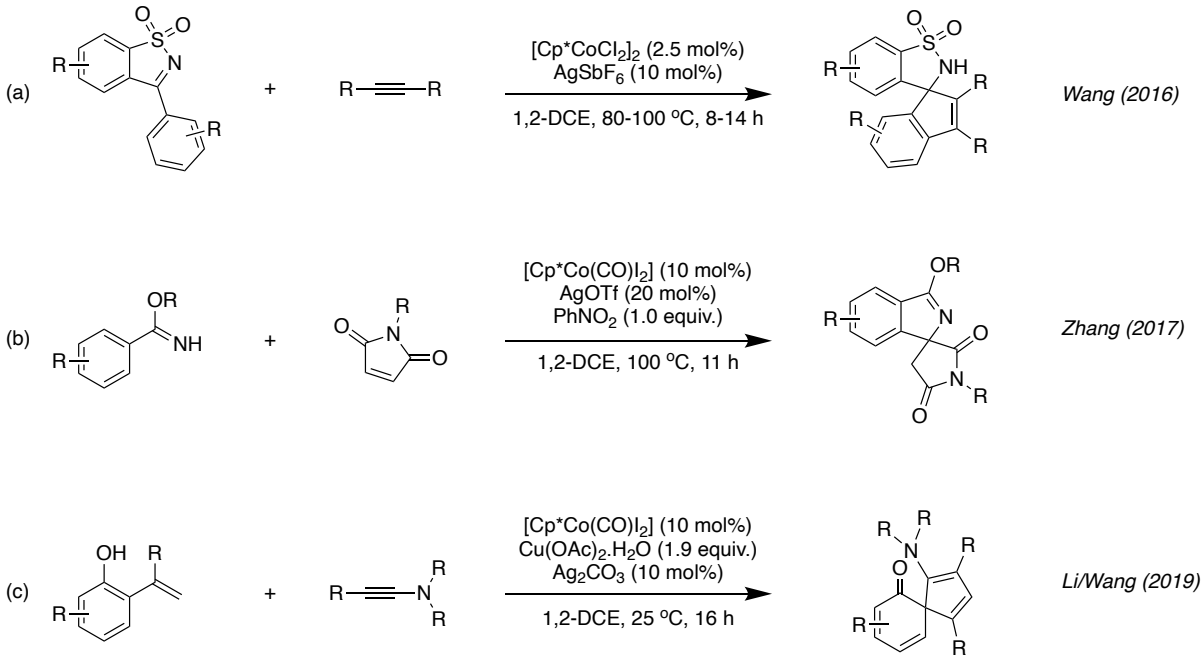


*Scheme 1.27 Cp*Co(III)-catalysed preparation of 2-aminobenzoxepines.*

2.4 Miscellaneous examples

2.4.1 Spirocyclic compounds

With the desire to exit “flat-land” in drug discovery programs, spirocyclic compounds have started to attract significant interest.[96] Without exception, Cp*Co(III) catalysis has been employed in this field, efficiently providing potentially useful additions to the landscape. In 2016, Wang reported on the coupling of *N*-sulfonyl ketimines with alkynes to realise spiro indenyl benzosultams (Scheme 1.28a).[97] The mechanism is redox neutral and follows that migratory insertion of an alkyne to the initial cobaltacycle formed by C-H activation results in a highly reactive species which through intramolecular addition generates the spirocyclic product. In a different approach, Zhang disclosed the use of benzimidates and maleimides for the preparation of spiro-cyclic heterocycles (Scheme 1.28b).[98] The authors proposed that after imidate-group directed C-H bond functionalisation, migratory insertion of the olefin and β-hydride elimination, an intramolecular aza-Michael addition of the alkenylated linear coupling product and the imidate furnishes the spirocyclic product. As a result of the β-hydride elimination step, the mechanism is Co(III)/Co(I)-based and the authors propose that TfOH is used to re-oxidise the Co(I) to Co(III). Interestingly, the spiro-lactam product could also be obtained through hydrolysis of the initially formed spirocyclic product. Most recently, Li and Wang have demonstrated the spiroannulation of 2-alkenylphenols with readily available ynamides (Scheme 1.28c).[99] The protocol was found to work well at room temperature and provides excellent regioselectivity, with a wide functional group tolerance. The authors propose that the phenol directs the C-H activation towards the alkyenyl protons, with a migratory insertion of the ynamide. After this step, isomerisation of the strained 8-membered metallocycle results in the loss of aromaticity forming the ketone moiety, before reductive elimination furnishes the final spirocyclic product.



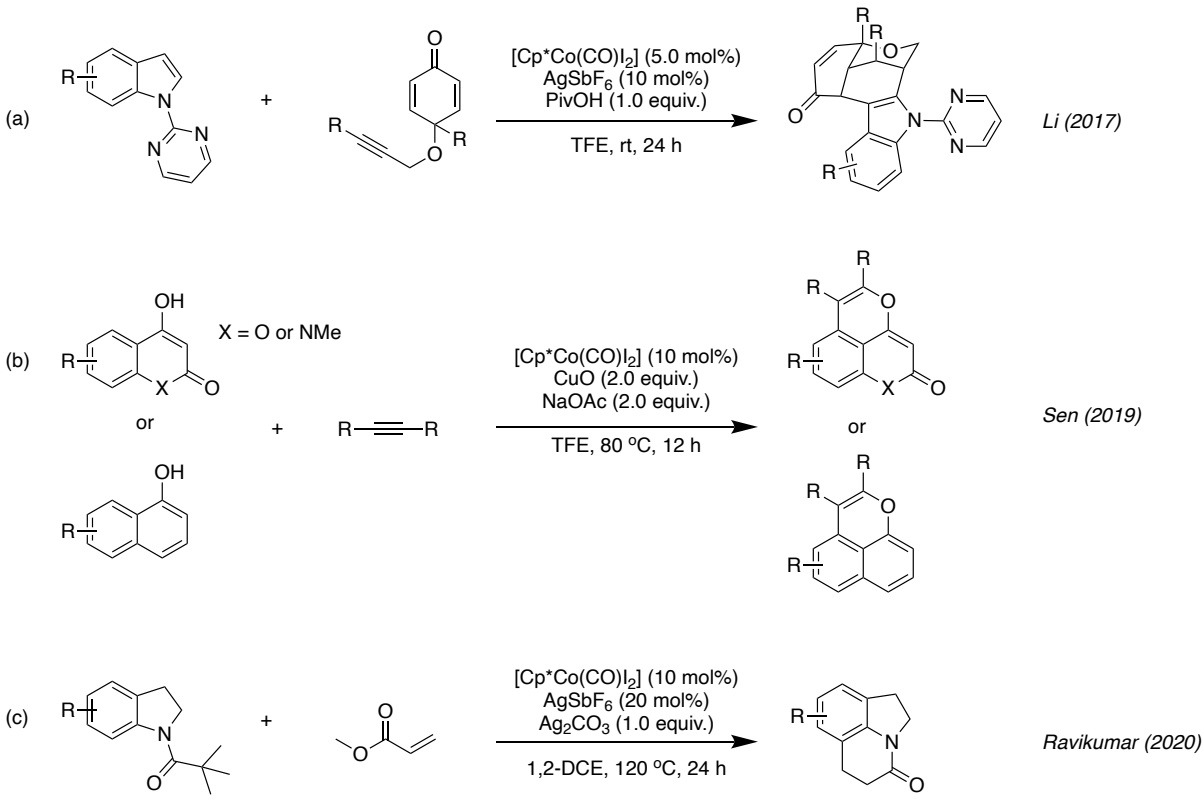
*Scheme 1.28 Access to diverse spirocyclic compounds using Cp*Co(III) catalysis.*

2.4.2 Others

Other examples of heterocyclic compounds which do not fit into the afore-discussed sections have also been described in the literature. Work from Li demonstrated the complexity that could be achieved through the coupling of readily available benzoindoles and 1,6-enynes (Scheme 1.29a).[100] In this work the direct comparison of Cp*Co(III) with Cp*Rh(III) catalysis was studied and it was found that different products were obtained. When Cp*Co(III) was utilised, 1,2-alkyne insertion occurred first, before an unusual intramolecular Diels-Alder reaction, which contrasts with Cp*Rh(III) where 2,1-alkyne insertion preferentially occurs. This work highlights the important differences between cobalt and rhodium, proving that cobalt is not simply a cheap replacement for rhodium.

In more recent work, Sen has reported the preparation of polycyclic pyrans (Scheme 1.29b).[101] The authors proposed a hydroxyl-assisted oxidative annulation mechanism; consisting of a deprotonated hydroxyl directed the C-H activation, before migratory

insertion and reductive elimination furnish the heterocyclic product. The mechanism is Co(III)/Co(I)-based and utilises Cu(II) as the terminal oxidant to provide the active catalyst species after reductive elimination. DFT calculations of important reaction intermediates were performed to support their mechanistic proposal. However, the authors choose not to connect the intermediates with appropriate transition states, and therefore failed to truly understand the operative mechanism. Finally, in 2020, Ravikumar developed a facile route for the synthesis of pyroquilons from readily available indolines (Scheme 1.29c).[102] The protocol operates through a one-pot manner through selective C(7)-H functionalization and concomitant cyclization, similar to the approach reported by Hamilton and Whiteoak (Scheme 1.26) for the synthesis of azepinones.



*Scheme 1.29 Cp*Co(III)-catalysed access to (a) complex heterocyclic fragments, (b) polycyclic pyrans and (c) pyroquilons.*

3 Conclusions and outlook

To conclude, this chapter has attempted to highlight some of the vast and rapidly expanding examples of the application of Cp*Co(III) catalysed C-H activation in the development of procedures for the formation of complex heterocycles. These results have all been disclosed very recently as researchers continue to exploit the potential of Cp*Co(III) catalysis. Indeed, in many cases the use of Cp*Co(III) catalysis allows new reactivity which is not observed with corresponding, more established, Cp*Rh(III) and Cp*Ir(III) analogues. The wide breadth of heterocycles now accessible through Cp*Co(III) catalysis points to the distinct possibility that this approach may soon become a new tool in the synthetic chemist's toolbox. Although, one of the remaining limitations is the lack of commercially available Cp*Co(III) catalysts, which is in contrast to the availability of Cp*Rh(III) and Cp*Ir(III) catalysts. Another important comment to be made is that, as with many areas within catalysis the mechanistic understanding from theory significantly lags behind the synthetic examples. The complex nature of the reaction mechanisms, and diversity within the directing groups and coupling partners, means that truly predictive models for reactivity are some way off. This is both a challenge for experimentalists and an opportunity for theoreticians. As has been highlighted in this chapter and other studies[103,104] the potential for Co(III) to access of high-spin states, or undergo SET-type reactions, opens the doors to a diverse range of non-classical pathways. From a theory perspective this can be problematic, as calculation of spin-state energetics has been shown to be highly functional dependant, and therefore a limitation of DFT. However, due to the size of experimentally relevant complexes, the use of multi-reference or coupled cluster methods throughout the entire reaction mechanism is impractical. The recently released open-shell DLPNO-CCSD(T) methods by Neese,[105] allowing for near couple

709 cluster accuracy on a DFT timescale, may well prove to be crucial in further
710 understanding these complex reaction mechanisms.

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