Recent advances using [Cp*Co(CO)I2] catalysts as a powerful tool for C-H functionalisation

CHIRILA, Paula G and WHITEOAK, Christopher <http://orcid.org/0000-0003-1501-5582>

Recent Advances using [Cp*Co(CO)I_2] Catalysts as a Powerful Tool for C-H Functionalisation

Paula G. Chirila and Christopher J. Whiteoak*

Expansion of the synthetic chemists' toolbox is currently a topic of great interest, with successes providing access to novel compounds and more efficient routes towards new and known pharmaceuticals and agrochemicals. In this context, the development and application of first-row transition metal-catalysed C-H functionalisation protocols is seen as a key opportunity. This perspective provides a brief background of the discovery and application of high-valent cobalt-catalysis in C-H functionalisation, before detailing examples of recent advances in this field using the powerful [Cp*Co(CO)I_2] catalysts for both terminal couplings and heterocycle formation. Finally, a discussion on the detection and isolation of elusive reactive intermediates in high-valent cobalt-catalysed C-H functionalisation, shedding light on how these catalyst systems operate, will be provided.

Paula G. Chirila is a PhD student at Sheffield Hallam University, UK. She received her MChem from the University of Bradford, UK, in 2015. Thereafter, she spent a year working as a junior researcher at UniCRE, Czech Republic, where her research focused on the development of fuels from second generation biomass, in the group of Dr. Kubicka and Dr. Kikhtyanin. In 2016, she joined the group of Dr. Whiteoak where her current research focuses on the application of high-valent cobalt-catalysed C-H functionalisation approaches for the development of novel synthetic protocols.

Dr Christopher J. Whiteoak is a lecturer in Inorganic Chemistry at Sheffield Hallam University. He received his MChem from the University of York (2004) and thereafter spent a period working for Unilever R & D. He completed his PhD studies under the supervision of Prof. Gibson FRS and Dr. Britovsek, in the field of oxidation catalysis, (Imperial College London, 2010). Thereafter he embarked on his postdoctoral career; Dr. Boisson at CPE-Lyon, researching in the field of polymerisation catalysis; Prof. Kleij at the ICIQ, developing new highly active catalyst systems for CO_2 utilisation; Dr. Ribas at the University of Girona, where he developed a keen interest in high-valent cobalt-catalysed C-H functionalisation. His current research focuses on the application of high-valent cobalt-catalysed C-H functionalisation for the preparation of relevant molecules.

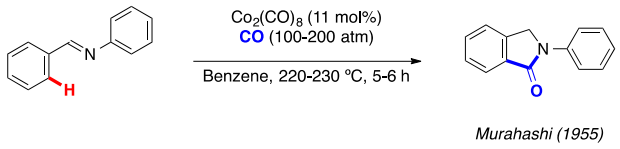
1. Introduction

Development of new methodologies for selective formation of bonds provides one of the key challenges/opportunities in modern day synthetic chemistry. Once developed, these technologies can enable controlled access to a range of important molecules from chemical intermediates and pharmaceuticals, to agrochemicals, amongst many others.

In this context, the development of transition metal catalysed methodologies has attracted significant attention, resulting from the often improved selectivities observed when compared with traditional organic synthetic routes. One of the most important contributions to the field of bond formation over recent decades, was the development of palladium cross-coupling, a field which continues to receive significant interest.[1] Since its conception, palladium cross-coupling has become a key tool in the synthetic chemists' toolbox. Indeed, the importance of these contributions to the field of bond formation was highlighted by the awarding of the 2010 Nobel prize to Heck, Negishi and Suzuki.[2] The major drawbacks of these palladium-catalysed bond forming reactions is the requirement for pre-functionalised substrates (eg. halides or triflates) and the production of halogenated wastes. One way of directly addressing these problems is to develop methodologies which employ a direct C-H activation step. In the case of palladium, significant advancements have been made in this field, providing protocols which no longer require pre-functionalised substrates and that produce less halogen-containing wastes.[3,4]

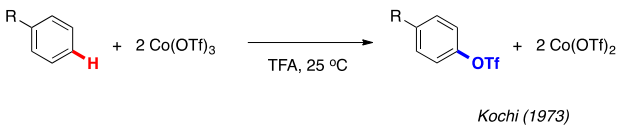
Whilst success in direct C-H functionalisation using palladium has been achieved, palladium itself is relatively expensive. As a result, a lot of attention has recently been directed towards the use of cheaper first-row transition metals, such as nickel and copper, and of particular interest to this perspective, cobalt.[5-8]

The identification of cobalt as a suitable metal for catalysing C-H functionalisation protocols is not entirely surprising given the relatively well developed field of rhodium-catalysed C-H functionalisation.[9,10] Researchers have in many cases taken the opportunity to reproduce some of these reactivities with significantly cheaper cobalt, which often, as will be discussed within this perspective, has led to unexpected and contrasting reaction outcomes. Cobalt-catalysed C-H functionalisation can be divided into two distinct categories; a low-valent approach (where the active cobalt catalyst is typically in the cobalt(0) or cobalt(I) oxidation state) and the high-valent approach (where the active cobalt catalyst is typically in the cobalt(III) oxidation state). From herein, we will use these definitions when discussing the different approaches to the use of cobalt in C-H functionalisation.



Murahashi (1955)

Scheme 1. Cobalt(0)-catalysed carbonylation of Schiff-bases for the formation of phthalimidines, *via* a C-H activation step, reported by Murahashi.



Kochi (1973)

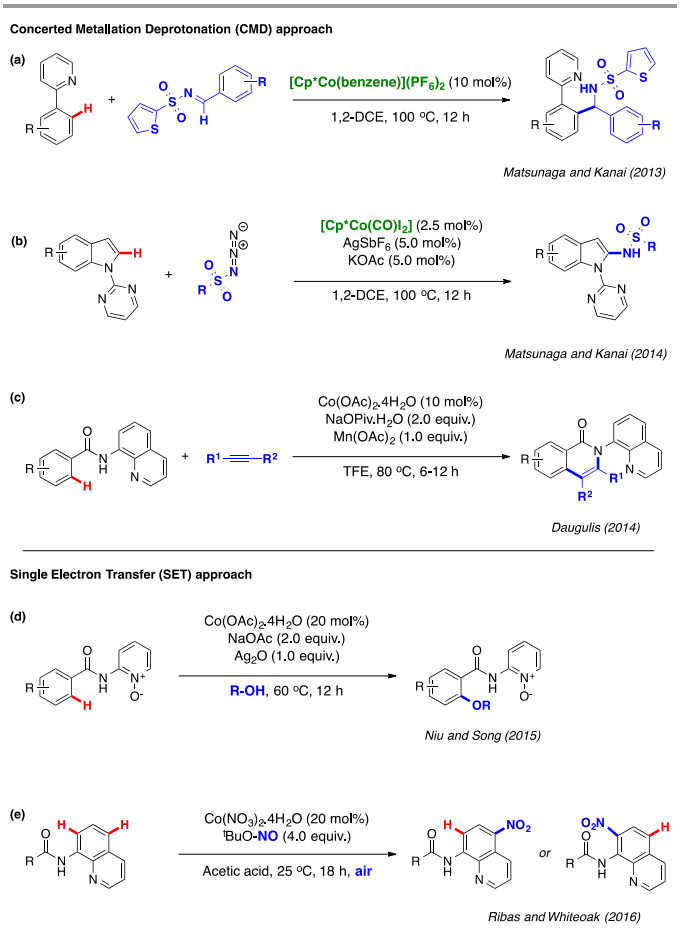
Scheme 2. Cobalt(III)-mediated trifluoroacetylation of aromatic compounds operating *via* a proposed SET mechanism, reported by Kochi and co-workers.

Cobalt-catalysed bond formation has been long known, with its origins being provided as far back as 1941 by Kharasch and Fields.[11] This early work reported the cobalt(II)-catalysed coupling of organic halides with Grignard reagents. Although not a C-H functionalisation protocol, it provided the first example of C-C coupling using cobalt catalysis. The first example of cobalt-catalysed C-H functionalisation came a few years later, in 1955, when Murahashi provided a low-valent cobalt-catalysed carbonylation protocol (Scheme 1).[12] This protocol provided access to phthalimidines through an annulation reaction of Schiff-bases and carbon monoxide, using $Co_2(CO)_8$ as catalyst.

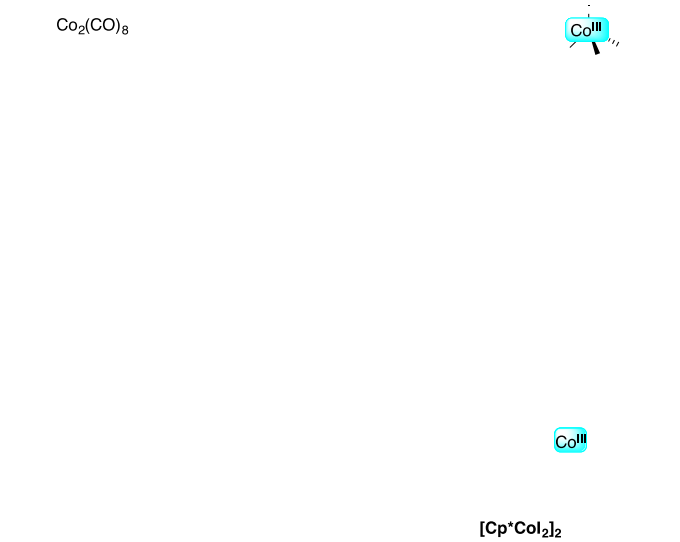
Since the first discovery of cobalt(0)-catalysed C-H functionalisation, the most significant applications of cobalt in catalysis have come in the fields of hydroformylation[13] and the development of the Pauson-Khand reaction.[14,15] It was not until 1973 that further advances in cobalt-catalysed C-H functionalisation were made. In this pioneering work, Kochi and co-workers presented the first example of a high-valent approach towards the preparation of aromatic trifluoroacetates through the functionalisation of aromatic substrates (Scheme 2).[16] Although a stoichiometric process requiring 2.0 equivalents of $Co(OTf)_3$ for each molecule of substrate and using trifluoroacetic acid (TFA) as solvent, the authors were able to study and elucidate a novel Single Electron Transfer (SET) mechanism for direct cobalt-catalysed C-H functionalisation.

Thereafter, the low-valent catalytic approach was further advanced by Kisch and co-workers in 1994,[17] reporting the *ortho*-alkenylation of aromatic azo compounds. This low-valent approach has since provided a significant number of potentially useful bond forming protocols, but is outside the scope of this perspective.[18,19] Meanwhile, development of catalytic protocols using high-valent approaches remained a significant hurdle to overcome, with only further proof-of-concept stoichiometric examples reported by Broderick/Legg and co-workers[20,21] and Avilés and co-workers.[22]

A significant catalytic breakthrough was made in the field by Matsunaga/Kanai and co-workers in 2013.[23] This work introduced the first Cp^*Co^{III}-type catalyst, whereby a $[Cp^*Co(benzene)](PF_6)_2$ complex was shown to catalyse the coupling of 2-arylpyridine substrates with sulfonyl imines and α,β-unsaturated ketones (Scheme 3a for sulfonyl imine example), the same group also extended this protocol to indole-based substrates soon afterwards.[24] More recently, in 2014, Matsunaga/Kanai and co-workers further disclosed that a $[Cp^*Co(CO)I_2]$ complex, in combination with a silver salt ($AgSbF_6$), displayed superior activity for a C-N bond forming protocol when compared to the $[Cp^*Co(benzene)](PF_6)_2$ catalyst (Scheme 3b).[25] This finding has since led to an explosion of interest in developing catalytic protocols based on the readily synthesisable $[Cp^*Co(CO)I_2]$ and related complexes (Scheme 4). This complex is analogous to the previously established and successful Cp^*Rh^{III}-type catalysts.[9] It should however be noted that successful coupling protocols have since been achieved using the $[Cp^*Co(benzene)](PF_6)_2$ catalyst,



Scheme 3. Examples of two distinct types of high-valent catalytic C-H functionalisation protocols using cobalt as catalyst. (a) First example of Cp*Co^{III}-type catalytic protocol. (b) First example of the use of [Cp*Co(CO)I$_2$] as catalyst. (c) First example of an 8-aminoquinoline assisted cobalt-catalysed protocol. (d) First example of a cobalt-catalysed SET approach. (e) First example of a remote C-H functionalisation utilising a cobalt-catalysed SET approach.



Scheme 4. (a) Preparation of [Cp*Co(CO)I$_2$] from $Co_2(CO)_8$.[25] (b) Preparation of [Cp*Co(MeCN)$_3$](SbF$_6$)$_2$ from [Cp*Co(CO)I$_2$].[27] (d) Preparation of [Cp*CoI$_2$]$_2$ from [Cp*Co(CO)I$_2$].[28]

particularly from the research groups of Kanai/Matsunaga and Ellman.[23,24,26]

Further development of the Cp*Co^{III}-type catalyst system has also led to the use of a single component catalyst, [Cp*Co(MeCN)$_3$](SbF$_6$)$_2$, precluding the use of silver salts in the reaction.[27] Interestingly, the corresponding dimeric complex, [Cp*CoI$_2$]$_2$, which can be easily prepared from [Cp*Co(CO)I$_2$] by refluxing in octane (Scheme 4c), has also been found to be active and in some cases, is found to be more active than the [Cp*Co(CO)I$_2$] catalyst.[28]

Around the same time as the development of the [Cp*Co(CO)I$_2$] catalyst, Daugulis and co-worker identified another route towards high-valent cobalt-catalysed C-H functionalisation with the aid of an 8-aminoquinoline directing group (Scheme 3c).[29] Whilst both of these approaches are proposed to proceed by a Concerted Metalation Deprotonation (CMD) process during the C-H activation step, examples of SET-based cobalt-catalysed C-H functionalisation protocols have also been reported. In 2015 Niu/Song and co-workers provided an example of the coupling of alcohols to aromatic and olefinic carboxamides, with the alcohol acting as both solvent and coupling partner (Scheme 3d).[30] During this work the authors made the unexpected discovery that the k_H/k_D value was approximately 1. This was an unusual result as in most other high-valent C-H functionalisation protocols, the C-H activation step is usually determined as the rate-limiting step, resulting in k_H/k_D values significantly higher than 1. Later, Niu/Wei and co-workers studied the mechanistic pathway of this conversion in further detail (DFT study) and confirmed that it most likely proceeds through the initially proposed SET mechanism.[31]

More recently, in 2016, Ribas/Whiteoak and co-workers provided the first example of a remote C-H functionalisation (nitration) of 8-aminoquinolines using a SET approach (Scheme 3e).[32] Again, in this report the C-H activation step was found not to be the rate limiting step, as the k_H/k_D value was approximately 1. This example is closely related to the mechanism proposed by Stahl and co-workers where copper is employed for the remote chlorination of 8-aminoquinoline compounds.[33] This cobalt-catalysed remote C-H functionalisation mechanism has more recently been expanded to perfluoroalkylation by Niu/Song and co-workers.[34]

Whilst recent reviews into the application of high-valent cobalt-catalysed C-H functionalisation[35] and more recently, specifically the Cp*Co^{III} catalysis have been published,[36,37] in this perspective the intention is to highlight the potential application of the related complexes [Cp*Co(CO)I$_2$], [Cp*CoI$_2$]$_2$ and [Cp*Co(MeCN)$_3$](SbF$_6$)$_2$ in a different way. This perspective will consider and group the specific substrates that have been utilised (Terminal couplings), whilst also showing the different routes towards heterocyclic products (Heterocycle formation). Finally, the perspective will provide a short discussion of recent examples of the characterisation of organometallic cobalt species, achieved through C-H activation, which are implicated as reactive intermediates in high-valent cobalt-catalysed C-H

functionalisation protocols. This overview is intended to be a thorough, but not exhaustive description of the state of [Cp*Co(CO)I_2] catalysed C-H functionalisation up to and including May 2017.

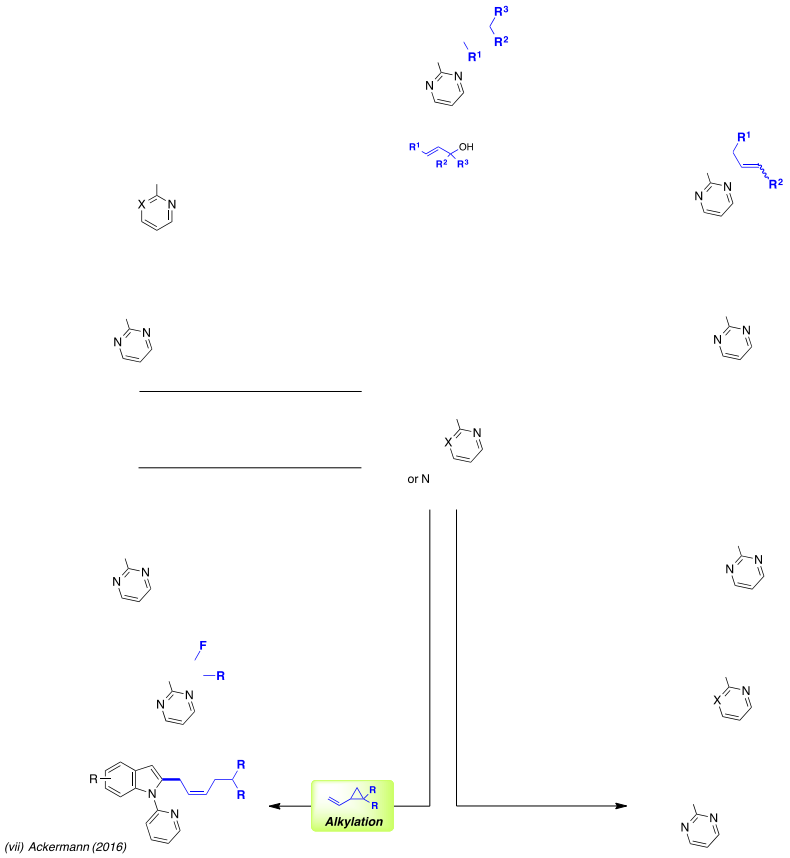
2. Terminal couplings using [Cp*Co(CO)I_2] catalysts

In this section, a wide range of examples of terminal couplings using [Cp*Co(CO)I_2] catalysts will be discussed. These couplings have been grouped by substrate type, allowing for a clear overview of the current state of the art. In many cases, couplings have been found to be substrate-type specific. This specificity/limitation can be exemplified by Wang and co-workers; in their recent article describing the trifluoromethylthiolation of 2-arylpyridines, where the catalytic protocol was unable to convert other common substrates, such as benzamides and an indole derivative containing a pyridine directing group.[38]

To date, indole derivatives with pyridine or pyrimidine directing groups have provided a significant number of examples of terminal couplings with the [Cp*Co(CO)I_2] catalyst. Herein, we will discuss couplings with indole-based substrates, followed by 2-arylpyridines/related compounds, and finally miscellaneous examples.

A. Examples using indole-based substrates containing pyridine and pyrimidine directing groups

The [Cp*Co(CO)I_2] catalyst has been demonstrated to be competent for a wide range of terminal couplings to indole-based substrates containing pyridine and pyrimidine directing groups (Scheme 5). Indoles bearing these directing groups can easily be prepared in high yield, through reaction of the indole with either 2-bromopyridine or 2-chloropyrimidine in the presence of sodium hydride. Furthermore, they can also be easily removed by heating with sodium ethoxide in DMSO. This directing group approach towards couplings to indoles provides specificity for couplings at the 2-position,



Scheme 5. Examples of reported C-C Couplings using indole-based substrates containing pyridine and pyrimidine directing groups. General conditions for each example: (i) 0.1 mmol substrate, 0.15 mmol allyl alcohol, 5.0 mol% [Cp*Co(CO)I_2], 10 mol% AgOTf, 10 mol% AgOAc, 1,2-DCE, 60 °C, 8 h. (ii) 0.40 mmol substrate, 0.80 mmol allyl carbonate, 0.5 mol% [Cp*Co(CO)I_2], 1.25 mol% $AgSbF_6$, 5.0 mol% PivOH, 1,2-DCE, rt, 4-24 h. (iii) 0.3 mmol substrate, 0.36 mmol α-diazomalonate, 5.0 mol% [Cp*Co(CO)I_2], 10 mol% $AgSbF_6$, 1,2-DCE, 100 °C, 20-48 h. (iv) 0.25 mmol substrate, 0.275 mmol alkyne, 2.5 mol% [Cp*CoI_2]$_2$, 10 mol% $AgSbF_6$, 2.0 equiv. K_2CO_3, TFE, 25 °C, 18 h. (v) 0.10 mmol substrate, 0.12 mmol hyper-valent iodine-alkyne reagent, 5.0 mol% [Cp*Co(CO)I_2], 10 mol% AgF, 3.0 equiv. $Mg(OCH_3)_2$, TFE, 110 °C, 24 h. (vi) 0.20 mmol substrate, 0.20 mmol phenylacetylene, 5.0 mol% [Cp*Co(CO)I_2], 10 mol% $AgSbF_6$, 1,2-DCE, rt, 10 min. (vii) 0.5 mmol substrate, 0.6 mmol vinylcyclopropane, 10 mol% [Cp*Co(CO)I_2], 20 mol% AgOTf, 20 mol% NaOPiv, 1,2-DCE, 50 °C, 20 h. (viii) 0.20 mmol substrate, 0.24 mmol *gem*-difluorostyrene, 5.0 mol% [Cp*$Co(MeCN)_3$]$(SbF_6)_2$, 2.0 equiv. $Ca(OH)_2$, TFE, 45 °C, 24 h. (ix) 0.20 mmol substrate, 0.25 mmol ketenimine, 2.5 mol% [Cp*Co(CO)I_2], 7.5 mol% $AgNTf_2$, 1,2-DCE, 80 °C, 10 h. (x) 0.50 mmol substrate, 0.72 mmol allene, 5.0 mol% [Cp*Co(CO)I_2], 10 mol% $AgSbF_6$, 1,2-DCE or 1,4-dioxane, 100-120 °C, 20 h. (xi) 0.25 mmol substrate, 0.45 mmol acrolein or α,β-unsaturated ketone, 2.5 mol% [Cp*Co(CO)I_2], 5.0 mol% $AgSbF_6$, 2.0 equiv. KOPiv, TFE, 70 °C, 16 h.

which is in contrast to traditional electrophilic substitution reactions which typically occur at the 3-position, thus providing new selectivity. This methodology was first described by Bergman and Venemalm in 1992, using carbon dioxide and lithium.[39] Herein, a selection of both C-C and C-X couplings will be discussed to exemplify the potential of the $[Cp^*Co(CO)I_2]$ catalyst for couplings at the 2-position of indoles.

C-C couplings. The first C-C coupling to indoles using the $[Cp^*Co(CO)I_2]$ catalyst was reported by Matsunaga/Kanai and co-workers in 2015.[40] This report described the dehydrative allylation of indoles with allylic alcohols (Scheme 5i). This conversion was found to be more efficient with $[Cp^*Co(CO)I_2]$ catalyst compared with the analogous $[Cp^*RhCl_2]_2$ catalyst. The reason for this is likely a result of the increased oxophillicity of the $[Cp^*Co]^{2+}$ cation compared with the $[Cp^*Rh]^{2+}$ cation, facilitating the dehydrative C-H allylation with allyl alcohols through a β-hydroxide elimination pathway, rather than a typical β-hydride elimination pathway. The reaction proceeds smoothly with good to excellent yields with a range of differently substituted indole substrates and allylic alcohols (both terminal and internal). The report also disclosed that a pyrrole bearing a pyrimidine directing group could also be converted, although this resulted in a double functionalisation at the 2 and 5-positons. Furthermore, 1-phenyl-pyrazole was also successfully converted under the optimised reaction conditions.

Shortly after this initial report, Glorius and co-workers extended the scope of this allylation protocol to the use of allyl carbonates as coupling partners (Scheme 5ii).[41] In this study, the authors noted that when the methyl carbonate was replaced with *tert*-butyl carbonate, the *E*/*Z* ratio could be increased, indicating that the conformation of the carbonate at the step of olefin insertion to the organometallic cobalt intermediate determines the relative configuration of cobalt and carbonate in the following intermediate and hence the geometry of the final olefin product.

Alkylation has been achieved using α-diazomalonates as coupling partners, reported by Wang and co-workers around the same time as the previous two examples (Scheme 5iii).[42] These α-diazomalonates have previously been shown to be excellent carbene precursors in transition-metal-catalysed carbene transfer reactions, generating highly reactive metal carbene species with extrusion of N_2.[43] The use of α-diazomalonates in C-H functionalisation has been previously reported by Yu and co-workers using the $[Cp^*RhCl_2]_2$ catalyst,[44] This cobalt-catalysed allylation methodology was found to be able to convert a wide range of substituted indoles, *N*-arylpyrazoles and even pyrrole itself, although another common substrate class, 2-arylpyridines, could not be converted. The authors also provided an intriguing example using β-methylindole, which provided an unexpected route towards the mono-ester through a proposed decarbalkoxylation step.

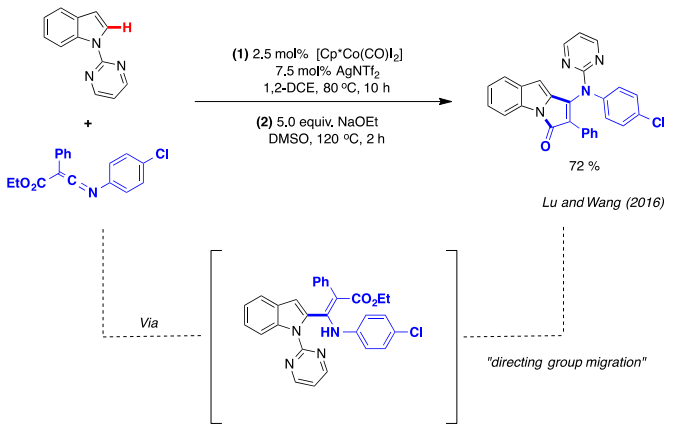
In addition to allylations, there are also reports of alkynylation protocols using the $[Cp^*Co(CO)I_2]$ catalysts. Both the groups of Ackermann and Shi have made contributions in this field. Alkynylations using bromoalkynes as coupling partners were reported by Ackermann and co-workers (Scheme 5iv),[45] with the conversion found to operate at room temperature. This protocol was also able to convert pyrroles with similar success and upon further increasing the bromoalkyne from 1.1 to 2.0 equivalents, dialkynylation of pyrrole was also achievable. In contrast, Shi and co-workers employed a different approach, using hyper-valent iodine-alkyne reagents (Scheme 5v)[46] in similarity to the previous $[Cp^*RhCl_2]_2$ catalysed example reported by Li and co-workers in 2014.[47] This protocol exhibited tolerance to a wide range of functionalised indoles, including β-cyanoindole. The drawback to this methodology is the elevated temperature when compared to the protocol of Ackermann and co-workers. Further use of alkynes as coupling partners was reported in 2016, whereby Chen/Yu and co-workers demonstrated that alkenylation could be realised when using phenylacetylene as the coupling partner (Scheme 5vi).[48] This reaction proceeded extremely rapidly, with almost quantitative yield after only 10 minutes at room temperature, although only one example is provided of indole substrates.

Vinylcyclopropanes have also been used as coupling partners in $[Cp^*Co(CO)I_2]$ catalysed C-C bond formation protocols. In 2016, Ackermann and co-workers presented an example of the coupling of vinylcyclopropanes with indole-based substrates bearing a pyridyl directing group (Scheme 5vii).[49] This protocol is notable as it delivers the thermodynamically less stable Z-alkenes with excellent diastereoselectivity. In particular, the amount of Z-alkene formed is significantly higher with $[Cp^*Co(CO)I_2]$ catalysis compared with corresponding rhodium catalysis. The authors also provided a mechanism which is evidenced by DFT studies, which indicates that the higher amount of Z-alkene with cobalt catalysis results from a shorter Co-C bond length in the Z-organometallic intermediate species.

The inclusion of fluorine atoms into organic molecules remains an important challenge in synthetic chemistry, enhancing the stability, lipophilicity and bioavailability of molecules. Li and co-workers have provided an intriguing example of an α-fluoroalkenylation using *gem*-difluorostyrenes as coupling partners (Scheme 5viii).[50] This protocol provides monofluoroalkenes with excellent Z-selectivity and yield. In this example the $[Cp^*Co(MeCN)_3](SbF_6)_2$ catalyst is used in order to eliminate the need for addition of a silver salt. The mechanism is proposed to pass through a key β-F elimination step and is similar to the $[Cp^*Rh(MeCN)_3](SbF_6)_2$ catalysed fluoroalkenylation reported by Feng/Loh and co-worker.[51] The optimised catalytic protocol is also able to convert compounds bearing other heterocyclic directing groups (Scheme 9xi).

The use of ketenimines as coupling partners for enaminylation was reported by Lu/Wang and co-workers (Scheme 5ix).[52] The products obtained from this protocol can be easily converted into 3*H*-pyrrolo[1,2-*a*]indol-3-ones, which are potentially important medicinal compounds, through a base-promoted cyclisation reaction in a second separate or

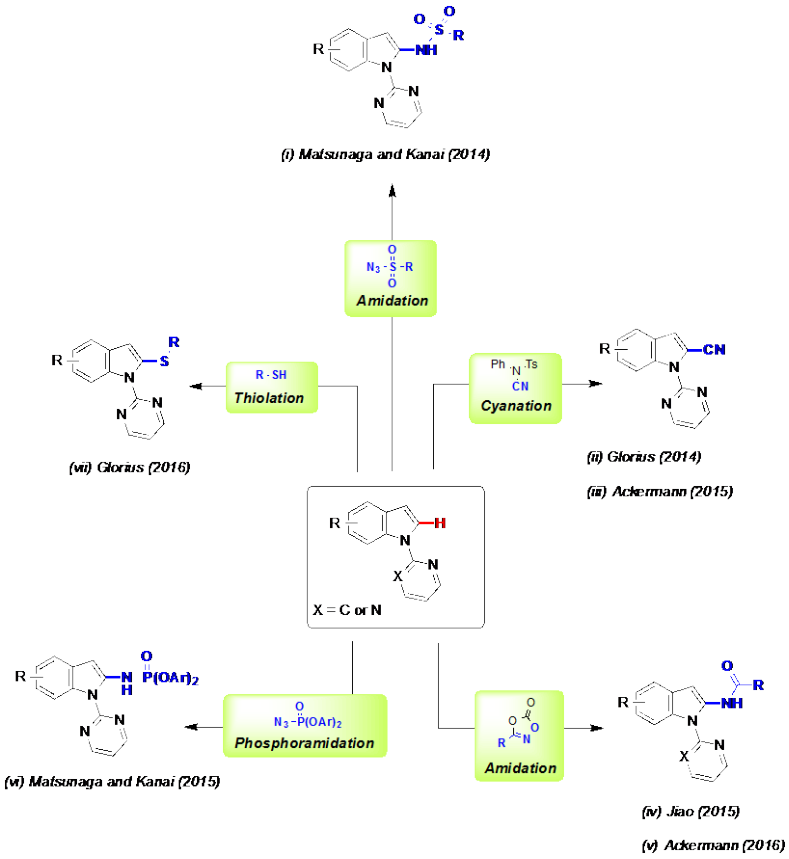
one-pot step (Scheme 6). This protocol demonstrates the potential of one-pot reactions for construction of compounds



Scheme 6. Example of a facile one-pot preparation of 3*H*-pyrrolo[1,2-*a*]indol-3-ones using cobalt-catalysed C-H functionalisation as the key step.

with high molecular complexity, using an initial cobalt-catalysed C-H functionalisation as the key step. In addition, the protocol is also able to convert indoline, pyrrole and phenyl substrates bearing the pyrimidine directing group, albeit in the case of indoline the conversion proceeds in relatively modest yield.

Recently, in 2017, the research groups of Ackermann and Li have reported [Cp*Co(CO)I_2] catalysed hydroarylation protocols (Scheme 5x and xi, respectively). Allenes were employed as coupling partners by Ackermann and co-workers providing α,β-unsaturated products.[53] In this report, the authors provide a detailed mechanistic and computational study, which combine to provide evidence for a mechanism which involves C-H cobaltation of the substrate, migratory insertion of the allene, intermediate isomerisation and a final proto-demetallation step. It was also shown to be possible to convert β-methylindole derivatives and also 2-phenylpyridine substrates (Scheme 9xiii). Meanwhile, Li and co-workers demonstrated that a variety of α,β-unsaturated ketones and glyoxylate could be used as coupling partners.[54] Competition experiments from this work provided several important findings; that glyoxylate is more reactive than the α,β-unsaturated ketones; acrolein is more reactive than α,β-unsaturated ketones; and that aryl-α,β-unsaturated ketones are less reactive than aliphatic-α,β-unsaturated ketones. Again, it was possible to convert β-substituted indole derivatives and the pyrrole derivative, albeit in modest yield.



Scheme 7. Examples of reported C-X Couplings using indole-based substrates containing pyridine and pyrimidine directing groups. General conditions for each example: (i) 0.20 mmol substrate, 0.30 mmol sulfonyl azide, 2.5 mol% [Cp*Co(CO)I_2], 5.0 mol% $AgSbF_6$, 5.0 mol% KOAc, 1,2-DCE, 100 °C, 12 h. (ii) 0.40 mmol substrate, 0.48 mmol *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS), 0.5-5.0 mol% [Cp*Co(CO)I_2], 1.0-10 mol% $AgSbF_6$, 2.0-10 mol% NaOAc, 1,2-DCE, 110 °C, 12-24 h. (iii) 0.50 mmol substrate, 0.75 NCTS, 2.5 mol% [Cp*Co(CO)I_2], 5.0 mol% $AgSbF_6$, 5.0 mol% KOAc, 1,2-DCE, 120 °C, 16 h. (iv) 0.20 mmol substrate, 0.22 mmol 1,4,2-dioxazol-5-one, 2.5 mol% [Cp*Co(MeCN)$_3$]$(SbF_6)_2$, 1,2-DCE, 80 °C, 12 h. (v) 0.50 mmol substrate, 0.60 mmol 1,4,2-dioxazol-5-one, 2.5-5.0 mol% [Cp*Co(CO)I_2], 5.0-10 mol% $AgSbF_6$, 5.0-10 mol% NaOAc, 1,2-DCE, 70-100 °C, 16 h. (vi) 0.80 mmol substrate, 0.40 mmol phosphoryl azide (yield based on phosphoryl azide), 5.0 mol% $[Cp^*CoI_2]_2$, 20 mol% $AgSbF_6$, 1,4-dioxane, 60 °C, 36 h. (vii) 0.50 mmol substrate, 1.0 mmol thiol, 10 mol% [Cp*Co(CO)I_2], 1.5 equiv. $Cu(OAc)_2$, 25 mol% $In(OTf)_3$, 1.25 equiv. benzoquinone, 1,4-dioxane, 60 °C, 5 h.

C-X couplings. In comparison to the number of C-C couplings which have been reported using the $[Cp^*Co(CO)I_2]$ catalyst, there are comparatively fewer examples of C-X couplings. Indeed, one of the key challenges in modern-day cross-coupling remains the selective formation of C-X bonds.

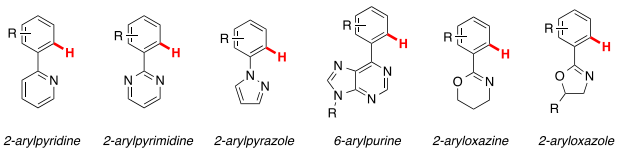
The first reported use of the $[Cp^*Co(CO)I_2]$ complex in catalytic C-H functionalisation was actually a C-X bond forming protocol, as previously mentioned. In 2014, Matsunaga/Kanai and co-workers demonstrated for the first time the increased efficiency of the $[Cp^*Co(CO)I_2]$ catalyst over the $[Cp^*Co(benzene)](PF_6)_2$ catalyst for the amidation of indoles bearing a pyrimidine directing group in combination with aryl/alkyl sulfonyl azides as coupling partners (Scheme 7i).[25] This conversion is analogous to the $[Cp^*Rh(MeCN)_3](SbF_6)_2$ catalysed protocol reported by Zhou/Li and co-workers in 2012.[55] Under the optimised conditions a wide range of substituted indoles and aryl/alkyl sulfonyl azides could be successfully coupled in excellent yields. More recently the same research group have extended the scope of this protocol towards the use of phosphoryl azides as coupling partners, although in this example 1,4-dioxane was found to be the optimal solvent in combination with the $[Cp^*CoI_2]_2$ catalyst (Scheme 7vi).[28]

In late 2014, both the groups of Glorius and Ackermann simultaneously reported a $[Cp^*Co(CO)I_2]$ catalysed cyanation protocol using *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) as cyanating agent (Scheme 7ii and iii).[27,56] In both examples the catalyst system tolerates a wide variety of substituted indoles and also β-methylindole. In addition, Ackermann and co-worker demonstrated that pyrrole and thiophenes could also be cyanated using the optimised catalytic protocol in good to quantitative yields.

Further examples of amidation protocols were developed using 1,4,2-dioxazol-5-ones as amidating agent, reported by Jiao and co-workers (Scheme 7iv).[57] This amidation agent is relatively facile to prepare and during the amidation reaction CO_2 is extruded as the only by-product. The optimised amidation protocol was also found to be able to convert a wide range of substrates (eg. 2-phenylpyridines, 6-arylpurines amongst others; see Scheme 9vi). This methodology was further exemplified by Ackermann and co-workers in 2016 (Scheme 7v), who also demonstrated conversion of phenyloxazolines and phenyloxazines, along with pyrrole (Scheme 9vii).[58]

Most recently, in 2016, Glorius and co-workers reported a thiolation protocol through the dehydrogenative cross-coupling with thiols (Scheme 7vii).[59] In addition to thiolation, this report also contains an example of selenation through use of diphenyl diselenide as coupling partner. Interestingly, when the $[Cp^*Co(CO)I_2]$ catalyst was not included in the reaction protocol, β-thiolation products were selectively obtained indicating the importance of cobalt catalysis to the reaction. In addition, the authors also attempted to provide insight into possible reaction intermediates, whereby analysis of the reaction mixture after 5 minutes using ESI mass spectroscopy revealed the presence of organometallic cobalt(III) intermediates.

B. Examples using 2-arylpyridine and related substrates



Scheme 8. Structures of 2-arylpyridine and related substrates.

2-arylpyridine and arylpyrimidine substrates have been extensively used in metal-catalysed C-H functionalisation studies to exemplify novel bond formation reactions, most likely as a result of the relative ease of converting this substrate due to its rigid nature. The field of $[Cp^*Co(CO)I_2]$ catalysed bond forming reactions is no exception to this, and a variety of interesting bond forming reactions have been reported using these and related substrates (Scheme 8 and 9).

Amidation of this class of substrate was first reported by Chang and co-worker in late 2014 (Scheme 9i).[60] This protocol uses acetoxycarbamates as a reactive source of amide, with the authors reporting that C-N bond formation was not achievable with sulfonyl azides (N_3-Ts; see Scheme 7i for previous successful application) using these substrate under the optimised reaction conditions. This exemplifies where protocols cannot be transferred to all classes of substrate. The protocol was found to be tolerant to a wide range of substituents on the aryl group and was also found to convert 6-arylpurine derivatives bearing sensitive functional groups, further enhancing the future applicability of the protocol.

Both the groups of Glorius and Ackermann have reported on the cyanation of 2-arylpyridines using NCTS (Scheme 9iv and v).[27,56] Glorius and co-workers have also reported an example of iodination and bromination of 2-aryl pyridines, although yields of the bromination product were found to be low (Scheme 9ii)).[27] In this example, *N*-iodosuccinimide (NIS) and *N*-bromophthalimide (NBP) were employed as iodinating and brominating agents respectively. A range of other substrates were studied and provided modest conversions, although indole substrates were not trialled in this halogenation study and it is not clear if this class of compound could be successfully converted under the optimised reaction conditions.

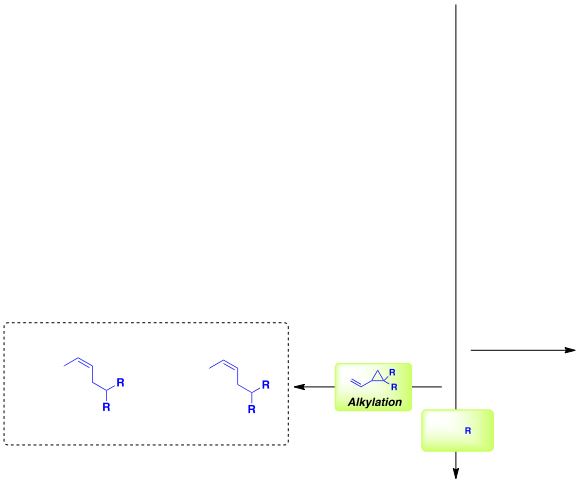
Further development and application of halogenation protocols has been achieved by Pawar and co-worker (Scheme 9iii).[61] This report describes the iodination and bromination of 6-arylpurines. Not only could the protocol covert 6-arypurines, it is also able to convert 2-thiophenepurines, although other heterocyclic purines could not be successfully converted.

In addition to the amidation protocol reported by Chang and co-worker (Scheme 9i), amidation of 2-aryl pyridines and additionally, 6-arylpurine derivatives has been reported by Jiao and co-workers (Scheme 9vi).[57] In contrast to

the Chang amidation protocol, this example uses a 1,4,2-dioxazol-5-one as amidating agent, extruding CO_2 as by-product. Aryl substrates using an oxime ether as directing group could also be converted in relatively modest yield. This conversion was also found to be more efficient when using the single component $[Cp^*Co(MeCN)_3](SbF_6)_2$ catalyst.

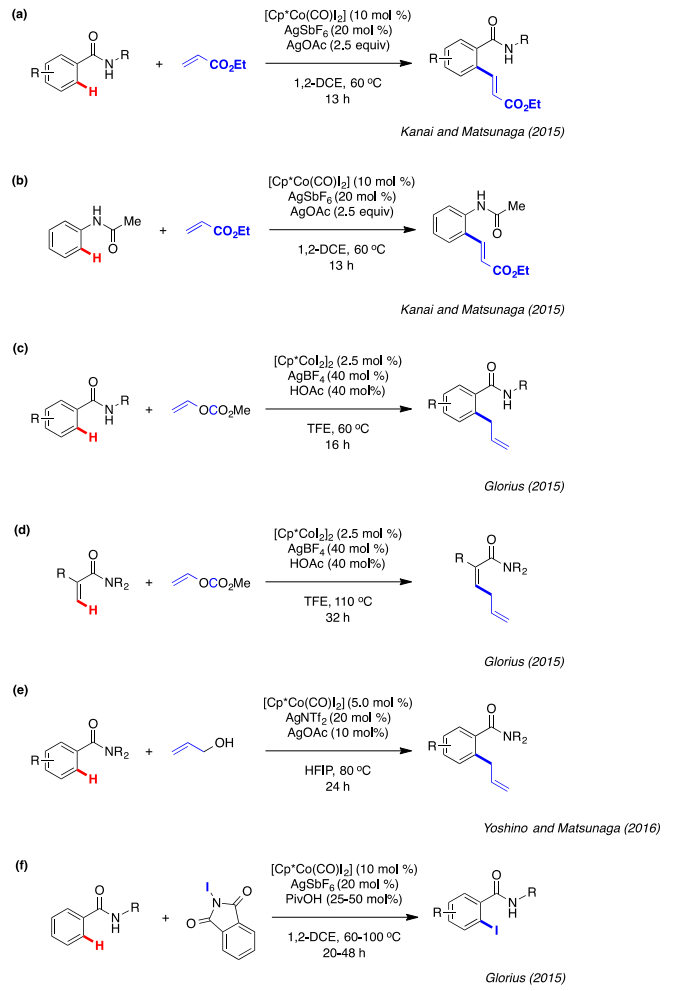
Substituted 2-aryl oxazolines are found in a number of bioactive compounds and in 2015, Ackermann and co-workers provided an example of the successful use of the oxazoline moiety as directing group for C-H functionalisation (Scheme 9vii).[58] The work demonstrated that this class of substrates could be amidated using the commonly applied 1,4,2-dioxazol-5-one compounds as amidating agent in combination with the $[Cp^*Co(CO)I_2]$ catalyst. The authors were also able to successfully use substituted oxazolines and oxazines as directing groups.

Alkenylation of 2-arylpyridines with terminal alkynes has been well studied by Chen/Yu and co-workers (Scheme 9viii).[48] In this report a range of substituted 2-arylpyridines and phenylacetylenes could be successfully coupled using the $[Cp^*Co(CO)I_2]$ catalyst. When 2-arylpyrimidine substrates were employed, mixtures of mono- and di-functionalisation products were obtained and upon doubling the loading of phenylacetylene, the yield of the di-functionalised product was enhanced, although a mixture was still obtained. The alkenylation protocol could also be transferred to 6-arylpurine derivatives.



Scheme 9. Examples of reported C-C and C-X Couplings using 2-arylpyridine and related substrates. General conditions for each example: (i) 0.10 mmol substrate, 0.11 mmol acetoxycarbamate, 8.0 mol% $[Cp^*Co(CO)I_2]$, 16 mol% $AgSbF_6$, acetone, 60 °C, 16 h. (ii) Iodination: 0.40 mmol substrate, 0.60 mmol *N*-iodosuccinimide (NIS), 10 mol% $[Cp^*Co(CO)I_2]$, 20 mol% $AgSbF_6$, 25 mol% NaOAc, 1,2-DCE, 70 °C, 20 h. Bromination: 0.80-1.20 mmol substrate, 0.40 mmol *N*-bromophthalimide (NBP), 10 mol% $[Cp^*Co(CO)I_2]$, 20 mol% $AgSbF_6$, 50 mol% PivOH, 60 °C, 36 h. (iii)) Iodination: NIS and Bromination: *N*-bromosuccinimide (NBS); 0.10 mmol substrate, 0.12 mmol NIS or NBS, 5.0 mol% $[Cp^*CoI_2]_2$, 20 mol% $AgNTf_2$, 20 mol% AgOAc, TFE, 80 °C, 12 h. (iv) 0.40 mmol substrate, 0.48 mmol *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS), 2.5-5.0 mol% $[Cp^*Co(CO)I_2]$, 5.0-10 mol% $AgSbF_6$, 5.0-10 mol% NaOAc, 1,2-DCE, 110 °C, 12-24 h. (v) 0.50 mmol substrate, 0.75 NCTS, 2.5 mol% $[Cp^*Co(CO)I_2]$, 5.0 mol% $AgSbF_6$, 5.0 mol% KOAc, 1,2-DCE, 120 °C, 16 h. (vi) 0.20 mmol substrate, 0.22 mmol 1,4,2-dioxazol-5-one, 2.5-5.0 mol% $[Cp^*Co(MeCN)_3](SbF_6)_2$, 1,2-DCE, 80 °C, 12 h. (vii) 0.50 mmol substrate, 0.60 mmol 1,4,2-dioxazol-5-one, 5.0 mol% $[Cp^*Co(CO)I_2]$, 20 mol% $AgSbF_6$, 20 mol% NaOAc, 1,2-DCE, 100 °C, 16 h. (viii) 0.20 mmol substrate, 0.20 mmol phenylacetylene, 5.0 mol% $[Cp^*Co(CO)I_2]$, 10 mol% $AgSbF_6$, 0.5 equiv. PivOH, 1,2-DCE, 60 °C, 5 h. (ix) 0.10 mmol substrate, 0.15 mmol allyl alcohol, 5.0 mol% $[Cp^*Co(CO)I_2]$, 10 mol% AgOTf, 10 mol% AgOAc, TFE, 60 °C, 8 h. (x) 0.5 mmol substrate, 0.6 mmol vinylcyclopropane, 10 mol% $[Cp^*Co(CO)I_2]$, 20 mol% AgOTf, 20 mol% NaOPiv, 1,2-DCE, 50 °C, 20 h. (xi) 0.20 mmol substrate, 0.24 mmol *gem*-difluorostyrene, 5.0 mol% $[Cp^*Co(MeCN)_3](SbF_6)_2$, 2.0 equiv. $Ca(OH)_2$, TFE, 45 °C, 24 h. (xii) 0.20 mmol substrate, 0.25 mmol ketenimine, 2.5 mol% $[Cp^*Co(CO)I_2]$, 7.5 mol% $AgNTf_2$, 1,2-DCE, 80 °C, 10 h. (xiii) 0.50 mmol substrate, 0.72 mmol allene, 5.0 mol% $[Cp^*Co^{III}(CO)I_2]$, 10-15 mol% $AgSbF_6$, 1,2-DCE or 1,4-dioxane, 100-120 °C, 20 h. (xiv) 0.20 mmol

substrate, 0.40 mmol $AgSCF_3$, 5.0 mol% $[Cp^*CoI_2]_2$, 20 mol% $NaOPiv.H_2O$, 1,2-DCE, 100 °C, 24 h. (xv) 0.40 mmol substrate, 0.60 mmol *N*-trifluoromethylthiodibenzenesulfonimide, 10 mol% $[Cp^*Co(MeCN)_3](SbF_6)_2$, 5.0 mol% $AgSbF_6$, 80 mg MS 3Å, 8 mL HFIP, 80 °C, 12 h.



Scheme 10. Examples of terminal couplings using benzamide substrates.

Yoshino/Matsunaga and co-workers have described the dehydrative C-H allylation of 6-aryl purines using allyl alcohols as coupling partners (Scheme 9ix).[62] The use of fluorinated solvent was found to be key, as the conversion was significantly retarded when using 1,2-DCE.

Ackermann and co-workers, Li and co-workers and Lu/Wang and co-workers and have also extended the application of their alkylation,[49] α-fluoroalkenylation[50] and enaminylation[52] protocols, to successfully include 2-arylpyridine and related substrates (Scheme 9x-xii). Although, the enaminylation protocol only provided products in modest yield compared with indole-based substrates containing a pyrimidine directing group. In a similar way, Ackermann and co-workers transferred their hydroarylation protocol to 2-aryl pyridine and 2-arylpyrimidine substrates (Scheme 9xii),[53] although again observing reduced yields compared to the same conversions with indole-based substrates containing pyrimidine directing groups.

Very recently, Wang and co-workers have presented the first trifluoromethylthiolation using $[Cp^*Co(CO)I_2]$ as catalyst (Scheme 9xii).[38] This conversion was found to only proceed with 2-arylpyridine and 2-arylpyrimidine substrates, with a range of other common classes of substrate (eg. indole-based substrates containing a pyrimidine directing group) the conversion failed. The optimised protocol provided a range of differently substituted trifluoromethylthiolated products in moderate yield. It was also found that both $[Cp^*Rh^{III}Cl_2]_2$ and $[Cp^*Ir^{III}Cl_2]_2$ were not competent catalysts for this conversion under the optimised conditions, demonstrating the sometimes differential activity of the $[Cp^*Co(CO)I_2]$ catalyst. It should however be noted that in this case the $[Cp^*CoI_2]_2$ dimer appears to show higher activity over the $[Cp^*Co(CO)I_2]$ catalyst. In a more recent report Yoshino/Matsunaga and co-workers have further extended the substrate scope and also included 6-arylpurines, employing *N*-trifluoromethylthiodibenzenesulfonimide as trifluoromethyl source (Scheme 9xiv).[63] The authors of this work also report that the single component catalyst, $[Cp^*Co(MeCN)_3](SbF_6)_2$, showed higher efficiency over the $[Cp^*Co(CO)I_2]/AgSbF_6$ catalyst system.

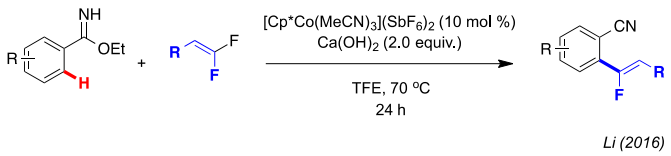
C. Miscellaneous examples

Besides the use of indole-based and 2-aryl pyridine/related substrates, couplings have also been successfully developed using other substrate classes. In this section, an overview of these couplings (not mentioned previously) will be presented.

Whilst cobalt-catalysed C-H functionalisation of benzamides is relatively well established using cobalt(II) salts, as a result of the pioneering work of Daugulis and co-worker,[29] there are few examples of terminal additions using the $[Cp^*Co(CO)I_2]$. In 2015 Kanai/Matsunaga and co-workers presented an example of C-H alkenylation of benzamides using ethyl acrylate (an allyl ester) as coupling partner (Scheme 10a).[64] In this example the authors propose that rather than the typical redox neutral catalytic cycle proposed in the majority of protocols using $[Cp^*Co(CO)I_2]$, there is a reductive elimination and hence the requirement for the super-stoichiometric AgOAc oxidant. This coupling was also able to be applied to acetanilides (Scheme 10b). In contrast, Glorius and co-workers reported a different reaction outcome by replacing the allyl ester with an allyl carbonate (Scheme 10c).[41] This latter protocol is also able to unusually convert alkenylamides (Scheme 10d), whilst replacement of the allyl carbonate with an allyl alcohol results in the same product, but significantly lower yield.

Yoshino/Matsunaga and co-workers have also provided a methodology for allylating benzamide substrates. This protocol employs allyl alcohols as allylating agents (Scheme 10e).[62] Using this methodology the authors were able to prepare a synthetically useful functionalised Weinreb amide.

In addition to these alkenylation and allylation reactions, Glorius and co-workers extended the substrate scope of their



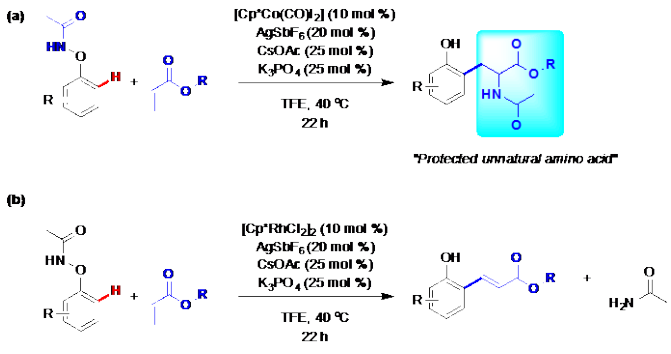
Scheme 11. Coupling of alkylbenzimidates with *gem*-difluoroalkenes reported by Li and co-workers.

iodination protocol to include benzamide substrates (Scheme 10f).[27] The authors also provided unusual examples of iodination of *N*-alkenylbenzamides, further demonstrating potential applicability.

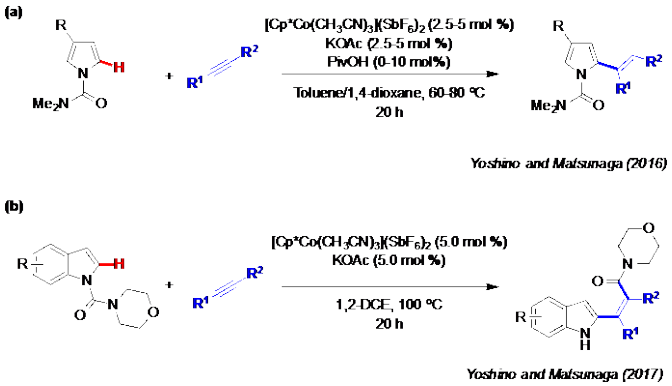
Whilst Li and co-workers were exploring the potential of their α-fluoroalkenylation using alkylbenzimidates, the authors observed an unusual product outcome (Scheme 11).[50] Rather than providing a simple terminal coupling as would be expected, the final product was actually a substituted benzonitrile, demonstrating further applicability of their protocol.

Glorius and co-workers have demonstrated application of the [Cp*Co(CO)I_2] catalyst for the facile formation of potentially relevant unnatural protected amino acids (Scheme 12).[65] The reaction proceeds by an intermolecular carboamination of the alkene, with the participating amine coming from a transfer from within the substrate itself. The authors also report contrasting reaction outcomes using Cp*Co^{III} and Cp*Rh^{III} catalysis, which is rationalised to result from the increased propensity for β-H elimination with rhodium.

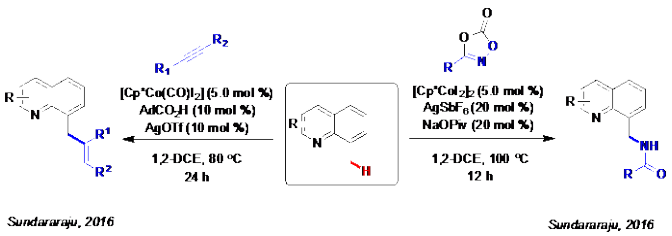
In 2016, Yoshino/Matsunaga and co-workers reported on the alkenylation of dimethylcarbamoyl-protected pyrroles (Scheme 13a).[66] The protocol was found to only mono-alkenylate at the 2-position or 5-position when unsymmetrically substituted pyrroles were employed. Under the optimised reaction conditions rhodium catalysts do not



Scheme 12. Example of differential outcome when coupling phenoxyacetamides with alkylacrylates using either cobalt or rhodium catalysts, reported by Glorius and co-workers.



Scheme 13. Alkyne coupling to (a) pyrrole and (b) indole, using carbomyl directing groups.



Scheme 14. C(sp^3)-H functionalisation using [Cp*Co(CO)I_2] and [Cp*CoI_2]$_2$ catalysts.

display any activity, again showing the distinct reactivity of Cp*Co^{III}. More recently, the same group provided a new coupling protocol with indole substrates bearing a carbomyl directing group with a range of alkynes. This new example also involved a directing group migration, providing access to a new family of tetrasubstituted alkenes (Scheme 13b).[67] Rhodium catalysts were again found not to catalyse this reactivity pattern, whilst this new report is in contrast to previous work where the same substrate was converted to pyrroloindolones using the [Cp*Co(benzene)]$(PF_6)_2$ catalyst.[68]

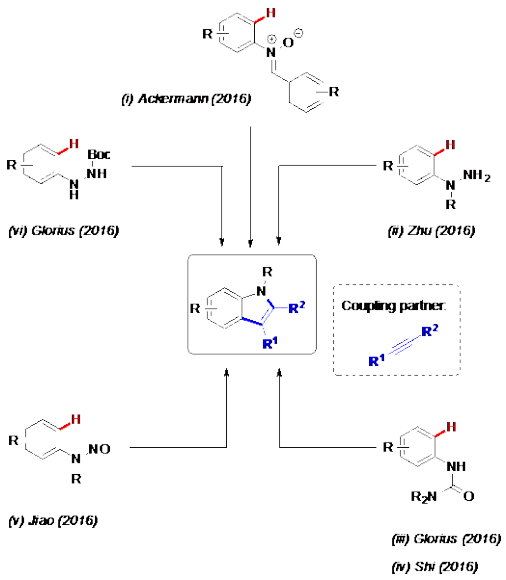
One of significant challenges in the C-H activation field concerns the functionalisation of C(sp^3)-H bonds. In 2016, Sundararaju and co-workers described the alkenylation and amidation of 8-methylquinoline substrates using the [Cp*Co^{III}(CO)I_2] catalyst (Scheme 14).[69,70] The alkenylation of this substrate builds on work reported by Wang and co-workers using [Cp*$RhCl_2$]$_2$ as catalyst.[71] Interestingly, [Cp*CoI_2]$_2$ was found to exhibit increased activity over the [Cp*Co(CO)I_2] catalyst for the amidation protocol.

3. Heterocycle formation using Cp*Co^{III} catalysis

Heterocyclic compounds are important motifs in a variety of key pharmaceutical and agrochemical compounds, with novel methods of for their preparation of great interest to the wider scientific community. Annulation reactions using alkynes as coupling partners are a powerful method for heterocycle formation and in this section, a diverse range of examples using [Cp*Co^{III}(CO)I_2] catalysts will be discussed. For clarity, the couplings have been grouped by product type, as protocols detailing the preparation of indoles and isoquinolines have received particular attention.

A. Protocols for the preparation of indoles

One of the first examples of C-H functionalisation using $[Cp^*Co(CO)I_2]$ for indole preparation was provided by Ackermann and co-workers in 2016 (Scheme 15i).[72] This report described the synthesis of indoles starting from nitrones *via* a C-H/N-O functionalisation process in a regioselective manner. After conducting competition experiments the authors disclosed that electron-rich nitrones were significantly more reactive under the protocol. Additionally, electron-rich alkynes were also found to be more active, suggesting a kinetically relevant alkyne coordination during the mechanism. Interestingly, under the optimised conditions, the $[Cp^*Co(CO)I_2]$ catalyst was found to be significantly more efficient compared to $[Cp^*RhCl_2]_2$, which has previously been

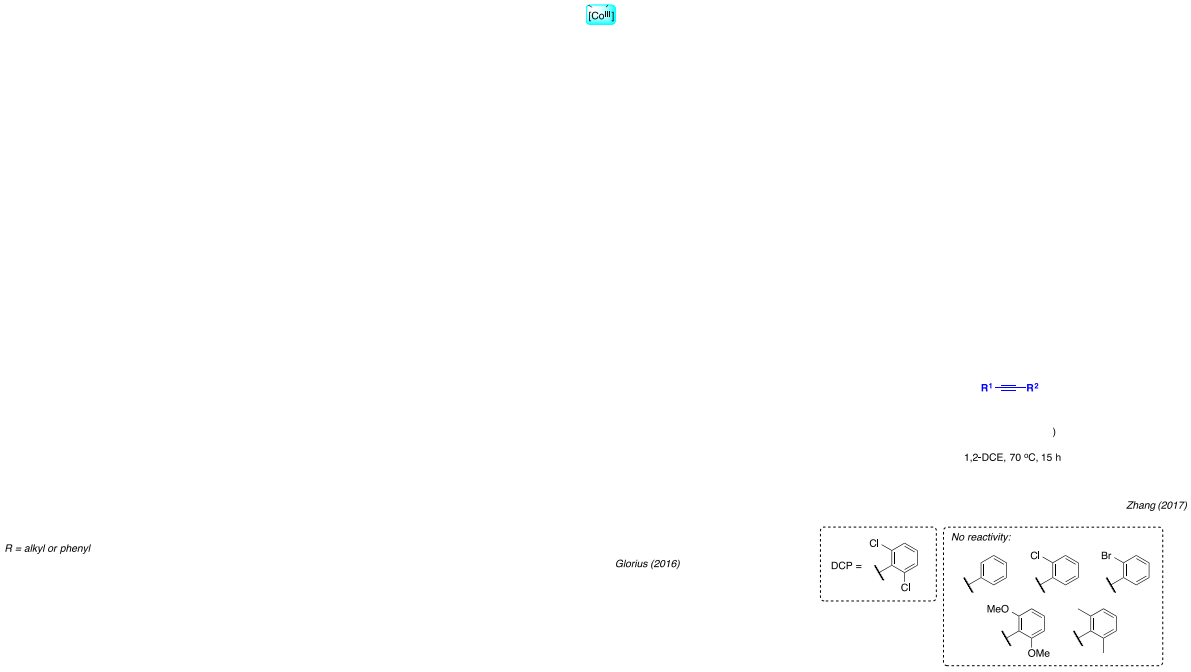


Scheme 15. Examples of preparation of indoles. General conditions for each example: (i) 0.50 mmol substrate, 0.75 mmol alkyne, 5.0 mol% $[Cp^*Co(CO)I_2]$, 20 mol% $AgSbF_6$, 20 mol%, HFIP, 100 °C, 16 h. (ii) 0.4 mmol substrate, 0.60 mmol alkyne, 2.0 mol% $[Cp^*CoI_2]_2$, 8.0 mol% $AgSbF_6$, 1.2 equiv. $Zn(OTf)_2$, 1,2-DCE, 50 °C, 12 h. (iii) 0.20 mmol substrate, 0.4 mmol alkyne, 10 mol% $[Cp^*Co(CO)I_2]$, 20 mol% $AgSbF_6$, 10 mol% $Fe(OAc)_2$, 1.0 equiv. Ag_2O, 1,2-DCE, 120 °C, 12 h. (iv) 0.10 mmol substrate, 0.15 mmol alkyne, 10 mol% $[Cp^*Co(CO)I_2]$, 20 mol% $AgSbF_6$, 2.0 equiv. NaH_2PO_4, 1.2 equiv. Ag_2CO_3, 1,2-DCE, 130 °C, 24 h. (v) 0.2 mmol substrate, 0.3 mmol alkyne, 5.0 mol% $[Cp^*Co(MeCN)_3](SbF_6)_2$, 2.0 equiv $Cu(OAc)_2$, 1,2-DCE, 80 °C, 24 h. (vi) 0.8 mmol substrate, 0.40 mmol alkyne (yields based on alkyne), 10 mol% $[Cp^*Co(CO)I_2]$, 20 mol% $AgSbF_6$, 10 mol% KOAc, HFIP, 80 °C, 22 h.

used to catalyse protocols for indole formation. Whilst cobalt also provides significant improvement in regioselectively when utilising unsymmetrical alkynes as coupling partners.[73] The authors also disclosed that the single component catalyst, $[Cp^*Co(MeCN)_3](SbF_6)_2$, was also able to efficiently provide indole products, thus removing the necessity for addition of a silver salt.

Zhu and co-workers have also reported an example of indole preparation utilising a cobalt-catalysed C-H activation approach (Scheme 15ii).[74] In this report arylhydrazines were used as substrates with both internal and terminal alkynes successfully employed. Excellent regioselectivity was again observed with this protocol and as mentioned, terminal alkynes could also be coupled, although in order to furnish improved yields it was necessary to use $[Cp^*Co(MeCN)_3](SbF_6)_2$. This necessity was in agreement with the authors previous similar work with rhodium, where the counterion was shown to inhibit activity.[75]

Simultaneously, both the groups of Glorius and Shi reported the use of *N*-arylureas as substrates for indole formation (Scheme 15iii and iv).[76,77] Both reports highlight the importance of a stoichiometric oxidant, indicating the likelihood of a key reductive elimination step in the mechanism. In addition, Shi and co-workers demonstrated that the use of less electrophilic ureas other than acetamides as directing groups is crucial for the reaction to proceed. In the absence of oxidant and addition of a Lewis acid, Glorius and



Scheme 16. (a) Different mechanistic pathways for the preparation of quinolines (Cycle **A)** and indoles (Cycle **B**) from the same starting material reported by Glorius and co-workers. (b) Reaction conditions reported for the preparation of indoles and quinolines. (c) Preparation of quinoline-*N*-oxide reported by Zhang and co-workers.

co-workers were able to selectively obtain quinolines, a transformation which will be discussed in the next part of this section. Shi and co-workers also observed a similar switch in reaction outcome when using acetanilide as substrate.

Jiao and co-worker have also reported a methodology for the preparation of indoles using *N*-nitrosoanilines as substrates (Scheme 15v).[78] The group reported that the $[Cp^*Co(CO)I_2]$ catalyst did not exhibit any reactivity for this reaction. As an alternative, the authors successfully employed the single component $[Cp^*Co(MeCN)_3](SbF_6)_2$ catalyst. It is worth mentioning that the lack of activity using $[Cp^*Co^{III}(CO)I_2]$ was not surprising considering that it was not used in the presence of a silver salt such as $AgSbF_6$. One key finding in this report was that alkynes bearing electron-deficient groups could be successfully employed as coupling partners, in contrast to unsuccessful reaction outcomes using $[Cp^*Rh(MeCN)_3](SbF_6)_2$. Furthermore, when using cobalt catalysis, the regioselectivity of the reaction is increased compared with corresponding rhodium catalysis.

In a final example, Glorius and co-workers, developed a protocol for indole preparation using an oxidising directing group, thus removing the requirement for an additional stoichiometric oxidant (Scheme 15vi).[79] This protocol was fully optimized and the most potent substrate was found to be the Boc-phenylhydrazine. Once again, the $[Cp^*Co(CO)I_2]$ catalyst proved to have superior reactivity compared to $[Cp^*RhCl_2]_2$.

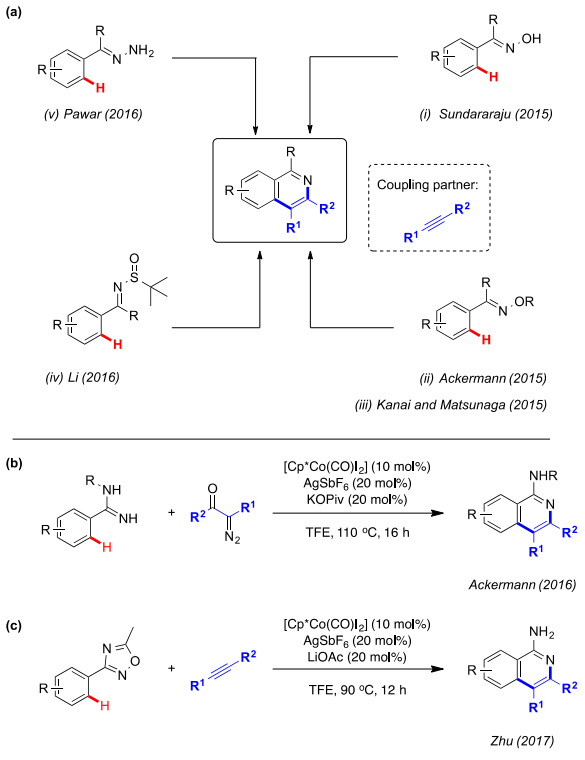
B. Protocols for the preparation of quinolines and isoquinolines

Before embarking on a discussion of the examples of quinoline and isoquinoline preparation using cobalt catalysis, the work of Glorius and co-workers demonstrating the preparation of indole/quinoline compounds should be first mentioned (Scheme 16b).[76] This work provides a mechanistic link between the two compound-types, both being annulation reactions using alkynes. In their report in 2016, Glorius and co-workers demonstrated that through control of the additive (either oxidant or Lewis acid), the formation of either indole or quinoline could be controlled (Scheme 16). It was also found that the R group of the amide was also important, with urea's reacting faster than alkyl amides in the indole synthesis protocol. This was reasoned to result from both a dehydrative (Scheme 16a, cycle A) and reductive elimination (Scheme 16a, cycle B) being key steps in the respective mechanisms, resulting in the realisation of two different products. Just before this report, Li and co-workers reported on the same transformation, albeit using different conditions (Scheme 16b).[80] This work provided a wide functional group tolerance, with relatively high regioselectivity when unsymmetrical alkynes were employed as coupling partners. The conversion did not occur when the pivaloyl or trifluoroacetyl amides were

used as substrates, indicating that electronic and steric effects of the amide group are important considerations.

More recently, Zhang and co-workers have disclosed a method for the preparation of quinoline-*N*-oxides through the coupling of arylnitrones with alkynes (Scheme 16c).[81] In this report, it was found that only 2,6-dichlorophenyl (DCP) and 2,6-difluorophenyl derivatives could be converted. The protocol displays a wide substrate scope, aside from the use of aliphatic alkynes and *ortho*-substituted arylnitrones, which result in low yield or no conversion, respectively. The quinoline-*N*-oxide product can easily be converted to the corresponding quinoline by reaction with sodium ethoxide in $PhCH_2OH$, whilst the *N*-oxide can also be used as a directing group for further transition metal-catalysed C-H functionalisation on the aryl-ring of the quinoline.

Isoquinolines are the building blocks for numerous pharmaceuticals thus; their synthesis has been of interest over the past few years. One of the first groups to have successfully synthesised isoquinolines *via* a high-valent cobalt C-H functionalization approach was Sundararaju and co-workers in 2015 (Scheme 17ai).[82] This was achieved by dehydrative annulation of oximes with different alkynes using $[Cp^*Co(CO)I_2]$. A notable observation is that the reaction took place without any external oxidants. The group confirmed that the OH group plays an important role in the catalytic cycle by replacing the OH with OMe and OAc, which dramatically reduced the yields of product. Various substituted oximes were used for the substrate scope, with high yields being obtained for *ortho*, *meta* and *para* substituted oximes. Furthermore, sterically complex substituents also provided high yields.



Scheme 17. (a) Examples of preparation of isoquinolines. General conditions for each example: (i) 0.2 mmol substrate, 0.24 mmol alkyne, 10 mol% $[Cp^*Co(CO)I_2]$, 20 mol% $AgSbF_6$, 20 mol% NaOAc TFE, 80 °C, 24 h. (ii) 0.50 mmol substrate, 0.75 mmol alkyne, 10 mol% $[Cp^*Co(CO)I_2]$, 20 mol% $AgSbF_6$, 20 mol% NaOAc, 1.2-DCE, 120 °C, 16 h. (iii) 0.15 mmol substrate, 0.18 mmol alkyne, 10 mol% $[Cp^*Co(CO)I_2]$, 20 mol% $AgSbF_6$, 20 mol% KOAc, 1,2-DCE, 80-120 °C, 24 h. (iv) 0.20 mmol substrate, 0.24 mmol alkyne, 10 mol% $[Cp^*Co(CO)I_2$, 20 mol% $AgNTf_2$, 1.0 equiv. HOAc, 1,2-DCE, 120 °C, 18 h. (v) 0.13 mmol substrate, 0.10 mmol alkyne (yield based on alkyne conversion), 10 mol% $[Cp^*Co(CO)I_2$, 20 mol% $AgSbF_6$, 25 mol% PivOH, TFE, 120 °C, 14 h. (b) Preparation of isoquinolines using diazo compounds. (c) Prepartion of 1-aminoisoquinolines, involving a directing group deacylation.

Almost simultaneous to this report, both Ackermann and co-workers and Kanai/Matsunaga and co-workers demonstrated that the OH group from oximes could be replaced with OAc to obtain high yields (Scheme 17aii and iii).[83,84] Interestingly, this latter report clearly focused on the use of terminal alkynes, providing significantly enhanced yields and site selectivity compared with the use of $[Cp^*RhCl_2]_2$.

In 2016, Li and co-workers provided a further example of isoquinoline preparation assisted by an oxidising N-S bond (Scheme 17aiv).[85] The catalytic reaction was found to tolerate a range substituents on the imine, thus expanding on the scope of previous reports in this field.

Another example of isoquinoline preparation using alkynes as coupling partners was reported by Pawar and co-workers (Scheme 17av).[86] In this report, easily prepared arylhydrazones were used as substrates, employing an N-N bond as an internal oxidant. In this protocol, terminal alkynes were not successfully converted.

All the $[Cp^*Co(CO)I_2]$ catalysed annulation reactions discussed so far have used alkynes as a coupling partner. In 2016, Ackermann and co-workers reported a different approach towards the preparation of isoquinolines *via* the reaction between aryl amidines with diazo compounds (Scheme 17b).[87] This protocol provides a novel route towards 1-aminoisoquinolines with significant substrate scope. It was noted that both electron donating and electron withdrawing groups were tolerated, although competition reactions demonstrated that substrates with electron donating functionalities were more easily converted than electron withdrawing ones.

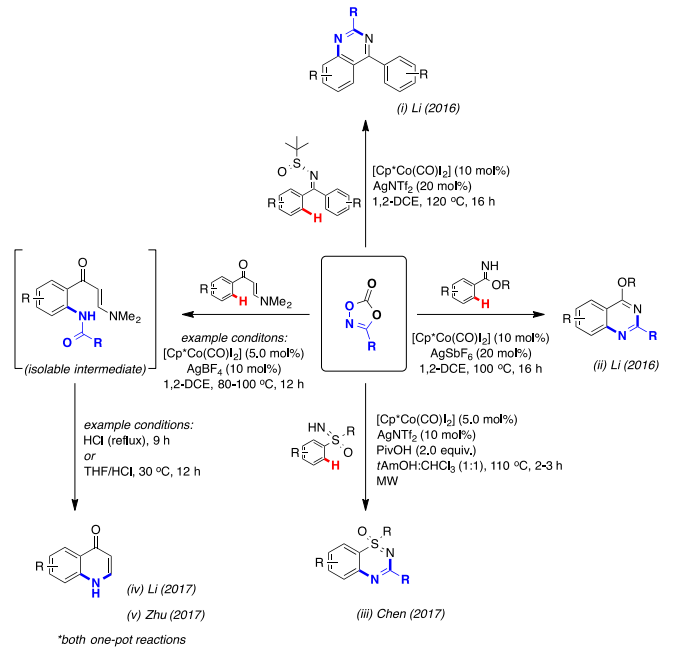
Most recently, in 2017, Zhu and co-workers have used aryloxadiazoles as substrates for the formation of 1-aminoisoquinolines, using alkynes as coupling partners (Scheme 17c).[88] The final product in this example is realised through a deacetylation of the directing group, providing access to potentially useful amino substituted isoquinolines. The protocol provides a wide substrate scope, although when unsymmetrical alkynes are used, the regioselectivity is modest.

C. Miscellaneous examples

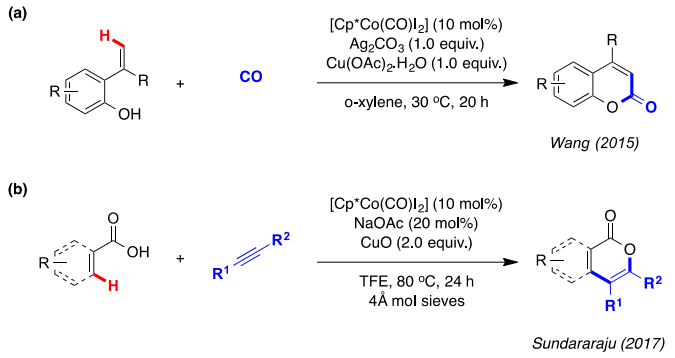
Even though significant attention has been paid to the synthesis of indoles, quinolines and isoquinolines, a range of other heterocycles have also been prepared using the $[Cp^*Co(CO)I_2]$ catalysts.

Whilst dioxazolones have been successful employed as coupling partners for terminal amidation protocols, they have also found utility as reagents for the synthesis of heterocyclic compounds (Scheme 18). To this end, in 2016**,** Li and co-workers described a first C-H functionalisation methodology for the preparation of quinazolines from both *N*-sulfinylimines and benzimidates using dioxazolones as

amidating agent (Scheme 18i and ii).[89] In this report, the authors use dioxazolones as nitrile sources, and disclose that in comparison, selectivity to the desired product was not successfully obtained using either iridium or rhodium catalysis. Both substrate types examined displayed wide substrate scope, resulting in the facile generation of two distinct families of quinazolines.



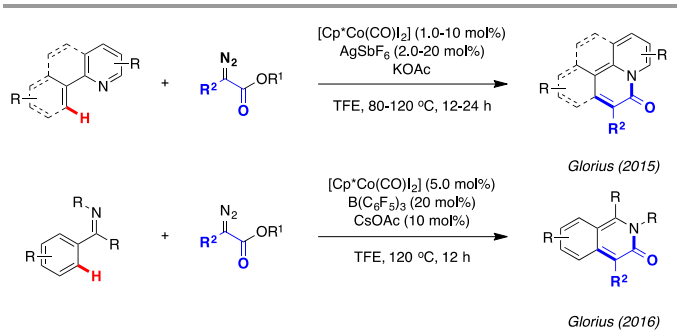
Scheme 18. Examples of heterocyclic compounds prepared using dioxazolones.



Scheme 19. Examples of coumarin and isocoumarin preparations.

More recently, Chen and co-workers reported on a microwave assisted preparation of thiadiazine-1-oxide compounds (Scheme 18iii).[90] Novel protocols for the synthesis of these compounds are highly desirable due to their properties as pharmaceutical agents, with current methodologies showing significant potential for improvement. Whilst Bolm and co-workers have provided a rhodium-catalysed protocol, significant organic waste is produced due to the necessary removal of a Boc group,[91] this new [Cp*Co(CO)I_2] catalysed methodology shows improvement over the rhodium example, producing only CO_2 and water as waste.

One-pot reactions, where sequential reactions can be performed without intermediate work-up, are gaining interest as purification is often costly and generates significant solvent wastes. The simplicity and power of the terminal amidating protocol lends itself well to being involved in one-pot reactions. In 2017, both the groups of Li and Zhu reported on one-pot procedures for the preparation of quinolone compounds starting from aryl enaminone substrates (Scheme 18iv and v).[92,93]



Scheme 20. Examples of protocols for the preparation of isoquinolin-3-ones using diazo compounds as coupling partners.

Both coumarin and isocoumarin compounds and their derivatives are recognised for their pharmacological and optical properties. In 2015, Wang and co-workers reported on the preparation of a range of coumarins through the coupling of CO with 2-alkenylphenols (Scheme 19a).[94] The annulation was achieved using only a balloon of CO and the potential applicability of this protocol was demonstrated through the rapid total synthesis of three natural products.

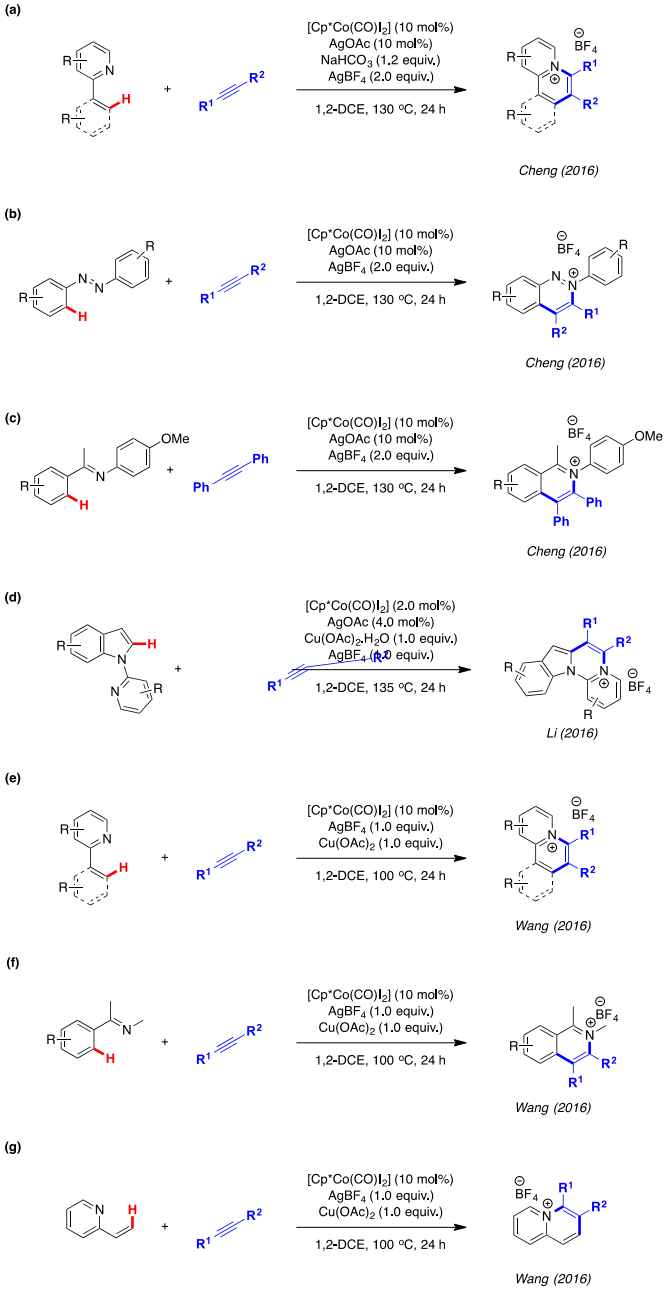
More recently, Sundararaju and co-workers have prepared isocoumarins through the annulation of readily-available carboxylic acids with alkynes (Scheme 19b).[95] The procedure displays a wide substrate scope and using this protocol it was possible to achieve the desired products from methacrylic acid, although low yields were obtained from acrylic acid. This is a rare example of carboxylic acid as a directing group in high-valent cobalt-catalysed C-H functionalisation protocols.

Using diazo esters as coupling partners, Glorius and co-workers have described two separate protocols for the preparation of isoquinolin-3-ones (Scheme 20).[96,97] In their first example, in 2015, a wide range of 2-arylpyridines were successfully annulated, providing highly conjugated isoquinolin-3-one derivatives. It was noted that all the compounds obtained were brightly fluorescent, resulting from their extended π-systems. It is proposed that the [Cp*Co(CO)I_2] catalyst is better suited to this conversion than [Cp*$RhCl_2]_2$, because the cobalt is able to act as both catalyst for the C-H activation step and, importantly, as a Lewis acid for the cyclisation step.

In their more recent example, the Glorius group have used imines as substrates, again taking advantage of diazo esters as highly reactive coupling partners. The protocol displays a wide substrate scope with good functional group tolerance. Addition of an external Lewis acid, $B(C_6F_5)_3$, was found to be key. This additive is suggested to play two distinct roles;

generation of the catalytically active cobalt species and acceleration of the C-H activation step.

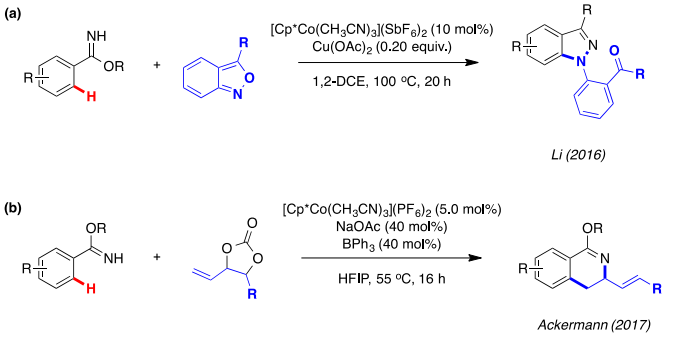
N-heterocyclic quaternary ammonium salts are found in the core structures of many bioactive compounds and pharmaceuticals. The synthesis of quaternary ammonium salts using the [Cp*Co(CO)I_2] catalyst was reported in 2016 for a diverse range of substrates by Cheng and co-workers, Wang and co-workers and Li and co-workers (Scheme 21).[98-100] In the work by Chen and co-workers (Scheme 21a-c),[98] 2-arylpyridines, azobenzenes, aryl ketimines and 2-vinylpyridines



Scheme 21. Examples of *N*-heterocyclic quaternary salts through alkyne annulation protocols.

were successfully annulated using alkyne coupling partners to provide the corresponding quaternary heteroaromatic ammonium salts, although regioselectivity was low when using unsymmetrical alkynes. The ammonium salt products could easily be converted, in high yield, into the corresponding amines. Furthermore, the products obtained from azobenzenes displayed strong blue photoluminescence with a narrow bandwidth, making them potentially interesting compounds for use in organic light-emitting diodes (OLEDs).

Li and co-workers employed a similar approach with the well-known indole-based substrates bearing a pyridyl directing group, providing access to a wide range of annulated ammonium salts, which again could be further converted to the corresponding amine through reduction with $NaBH_4$



Scheme 22. Examples of heterocyclic compounds derived from aryl imidates.

(Scheme 21d).[99] The authors reported substitution on the pyridyl directing group enhanced or suppressed catalytic activity. Including a methyl group at the C-2 or C-3 position affords high yields of product, whilst including a methyl group at the C-1 or C-4 positions completely inhibited reactivity.

In addition, Wang and co-workers have also provided a route to several different heterocyclic quaternary ammonium salts (Scheme 21e-g).[100]

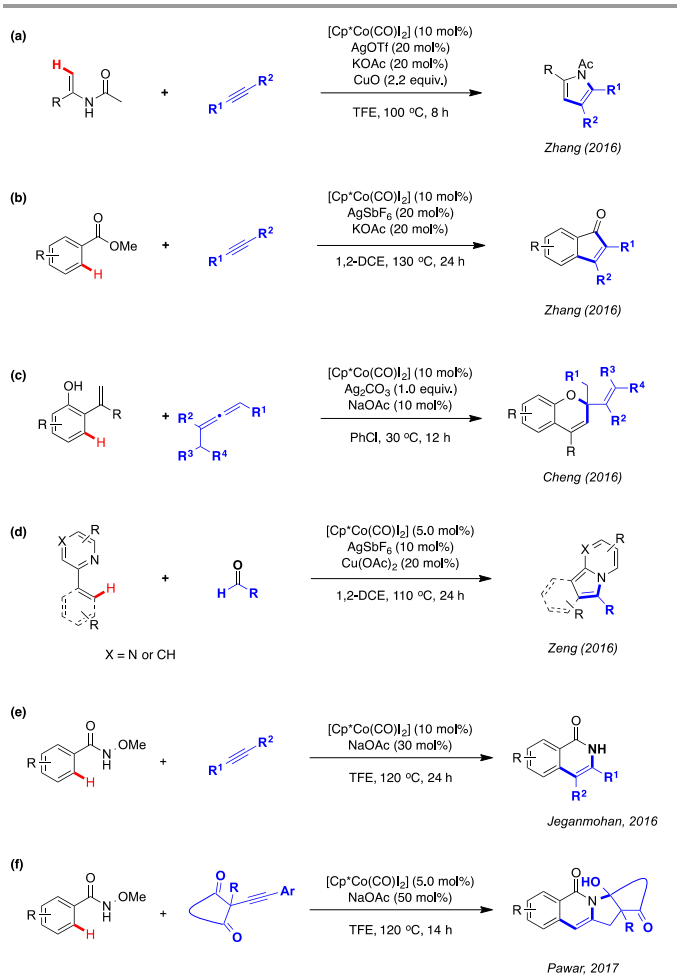
Li and co-workers have used anthranils as coupling partners with aryl imidate substrates to access 1*H*-indazoles (Scheme 22a).[101] In this example the anthranil coupling partner also acts as an organic oxidant. The single component [Cp*Co(MeCN)$_3$](SbF$_6$)$_2$ catalyst provided enhanced yields over the [Cp*Co(CO)I_2]/AgSbF$_6$ catalyst system. The authors also suggest that the N-N bond formation likely involves a nitrogen radical intermediate species formed by a SET step, resulting from the catalytic amounts of copper used in the protocol.

Vinylethylene cyclic carbonates (VEC's) have shown significant potential as coupling partners in several synthetic protocols as a result of their facile preparation and, analogously to dioxazolones, only releasing CO_2 as waste.[102-104] Recently, Ackermann and co-workers have used aryl imidate substrates and VEC's to provide an unusual domino C-H/N-H allylation (Scheme 22b).[105] During optimisation studies the use of either [Cp*Co(CO)I_2] or the single component [Cp*Co(MeCN)$_3$](SbF$_6$)$_2$ furnished low yields of the annulated product. In contrast, high yields were obtained when the single component catalyst, [Cp*Co^{III}(MeCN)$_3$](PF$_6$)$_2$, was employed. It is also noteworthy that rhodium catalysis was observed to be less efficient than cobalt catalysis for this conversion.

The synthesis of pyrroles has attracted interest because of they are building blocks for a number of medicinal compounds.

In 2016, Zhang and co-workers developed a [Cp*Co(CO)I_2] catalysed approach for the facile preparation of multi-substituted pyrroles by coupling enamides with alkynes (Scheme 23a).[106] The catalytic system showed high tolerance for various electron withdrawing and electron donating groups and can be operated on a gram-scale. However, alkyl substituted enamides were found to afford lower yields due to decomposition. Compared with analogous palladium catalyst systems, this new protocol presents increased regioselectivity.[107,108]

Zhang and co-workers have also developed a protocol for the preparation of indenones from readily available benzoic



Scheme 23. Further examples of heterocyclic compound preparation using cobalt catalysis.

esters and alkynes (Scheme 23b).[109] The [Cp*Co(CO)I_2] catalyst was found to display unique reactivity over the [Cp*$Rh^{III}Cl_2$]$_2$ catalyst for this conversion. Unfortunately, the regioselective coupling of unsymmetrical alkynes presents a challenge that the optimised catalyst system was unable to overcome, providing a future opportunity for further improvement of this protocol.

Whilst there are a significant number of reported couplings for forming heterocyclic products using alkynes as coupling partners, the potential of allenes has been relatively overlooked. Cheng and co-workers have developed a protocol for the preparation of *2H*-chromenes *via* a facile coupling of 2-vinylphenols with allenes, where the allene is a one-carbon coupling partner (Scheme 23c).[110] This was the first example that used allenes for couplings with [Cp*Co(CO)I_2] in catalysed C-H functionalisation protocols. The scope of 2-vinylphenols revealed generally high yields, but electron-donating methoxy substituents resulted in significantly reduced yields. The mechanism is proposed to proceed *via* the C-H activation of the vinyl group, allene insertion and a final intramolecular regioselective phenoxide addition.

Coupling of aldehydes with 2-aryl pyridines and 2-alkenyl pyridines, furnishing indolizines has been reported by Zeng and co-workers (Scheme 23d).[111] In this example, as with the example of Glorius previously (Scheme 20), the authors suggest that the cobalt catalyst is playing the dual role of both C-H activation and Lewis acid catalyst. The protocol displays excellent functional group tolerance with respect to the substrate, but clear limitations were observed when examining the aldehyde scope. Ethyl oxoacetate, oxo-aryl acetaldehyde and oxo-alkyl acetaldehyde were successfully coupled, but aldehydes such as benzaldehyde and acetaldehyde were not suitable for the optimised protocol. This example is similar to work reported by Ellman and co-worker, using the [Cp*Co(benzene)]$(PF_6)_2$ catalyst.[26a]

Jegamohan and co-workers have reported the annulation of *N*-methoxybenzamides with alkynes (Scheme 23e).[112] The authors demonstrated that the isoquinolone products could easily be converted into potentially useful 1-halo substituted isoquinoline derivatives using either PBr_3 or $POCl_3$ for bromo- and chloro- products, respectively. In another example, Pawar and co-workers have recently described a facile route towards indolizidines (Scheme 23f).[113] The protocol utilises readily prepared aryl amides and alkynediones as coupling partners. The reaction tolerates both electron-withdrawing and electron-donating functional groups. It is notable that the group used the optimised conditions for late-stage functionalisation of estrone derivatives. Both of these reports are intriguing interesting as they do not require addition of any silver salts even though the [Cp*Co(CO)I_2] catalyst is employed.

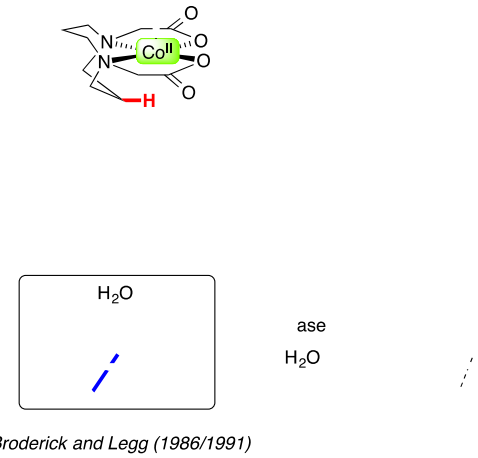
4. Experimental evidence for organometallic intermediates in cobalt-catalysed C-H functionalisation protocols

Even though high-valent approaches towards cobalt-catalysed C-H functionalisation are advancing at a rapid rate, surprisingly little attention has been directed towards either the detection or isolation of the commonly proposed Co(III) organometallic intermediate species. Indeed, to the best of our knowledge there is only one report of a Cp^*Co^{III} organometallic complex formed by a direct C-H activation event. In 2001, Avilés and co-workers demonstrated that reaction of [Cp*Co(PPh_3)I_2] with an azobenzene substrate, in the presence of $AgBF_4$, furnished the corresponding cyclometallated product (Scheme 24).[22] Conclusive evidence for the formation of the organometallic

product was provided by X-ray crystallographic and multinuclear NMR studies. It should be noted that once isolated no further reactivity studies were attempted. More recently, Kanai/Matsunaga and co-workers have isolated a cobaltocycle using the 2-phenylpyridine substrate, although they authors prepared the compound by a transmetallation using an organozinc species and not a direct C-H activation.[69]

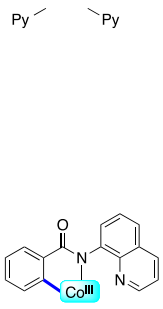
Other examples of isolation of organometallic cobalt species prepared through direct C-H activation have been obtained starting from cobalt(II) salts or cobalt(II) coordination compounds. As long ago as 1986, Broderick/Legg and co-workers isolated organometallic cobalt species using a quadridentate macrocycle ligand, "dacoda" (1,5-diazacyclooctane-*N*,*N'*-diacetic acid).[20,21] In this work, the authors were also able to identify a weak agostic interaction between the intermediate cobalt(III) coordination complex and the hydrogen atom to be abstracted (Scheme 25). This agostic interaction was identified from the X-ray structure of the cobalt(III) coordination compound. This work indicates that cobalt(III) is the actual species which activates the C-H bond, through a weak two-electron, three-centre intermediate.

Scheme 24. Preparation of a Cp*Co^{III} organometallic complex formed by a direct C-H activation.



Broderick and Legg (1986/1991)

Scheme 25. Stepwise organometallic cobaltation described by Broderick/Legg and co-workers.



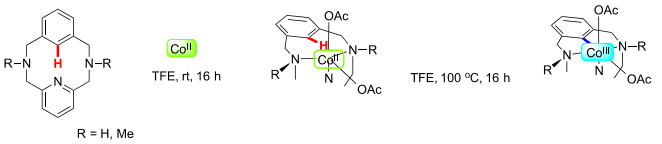
s (2016)

Isolated and characterised (including X-ray crystal structure)

Scheme 26. Detected/isolated organometallic cobalt(III) species containing the 8-aminoquinoline directing group.

Over recent years several groups have either isolated or obtained mass-spectrometric evidence of organometallic cobalt(III) intermediates using substrates bearing the 8-aminoquinoline directing group (Scheme 26).[29,114-116] All of these reports utilise cobalt(II) salts, hence requiring an in-situ oxidation of the cobalt, as was observed in the example of Broderick/Legg and co-workers. In these studies, Maiti and co-workers have also proved that their isolated intermediate was catalytically competent.

Most recently, Ribas and co-workers have provided an extensive study into the formation of organometallic cobalt species in C-H functionalisation protocols.[115] In this work a macrocyclic platform was used to stabilise the organometallic intermediate resulting from the C-H activation of an C(sp^2)-H bond (Scheme 2). The authors were able to isolate and thoroughly characterise both the cobalt(II) co-ordination complexes and also the organometallic cobalt(III) species, including X-ray crystal structures and an EXAFS study. Furthermore, reactivity studies using alkynes as coupling partners provided important insights into high-valent cobalt-catalysed annulation protocols which operate through a key C-H activation step.



Scheme 27. Stepwise cobaltation described by Ribas and co-workers.

5. Summary and outlook

Over the past few years, there has been an explosion in the use of [Cp*Co(CO)I$_2$] catalysts in direct C-H bond functionalisation protocols, since the initial report by Kanai and Matsunaga. In many cases this powerful cobalt catalyst

presents differing reactivity profiles to analogous rhodium catalysts. This is likely due to the lower electronegativity and increased Lewis acidity of cobalt compared to rhodium and a number of researchers have used this to their advantage when designing new catalytic protocols. Furthermore, the cost and relative low toxicity of cobalt make this an appealing metal to use. Whilst significant strides are being made with individual couplings, and as some groups have demonstrated, integration of [Cp*Co(CO)I_2] catalysed reactions into multi-step one-pot procedures to provide rapid and facile access to highly complex molecules remains an intriguing opportunity. Whilst, significant attention should also be directed to the development of highly challenging, yet potentially powerful C(sp^3)-H functionalisations.

Given the still unexplored full potential of [Cp*Co(CO)I_2] catalysts, we expect that new exciting and diverse protocols will be developed over the coming years using the [Cp*Co(CO)I_2] catalysts, making cobalt catalysed C-H functionalisation a key tool in the synthetic chemists' toolbox.

Acknowledgements

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