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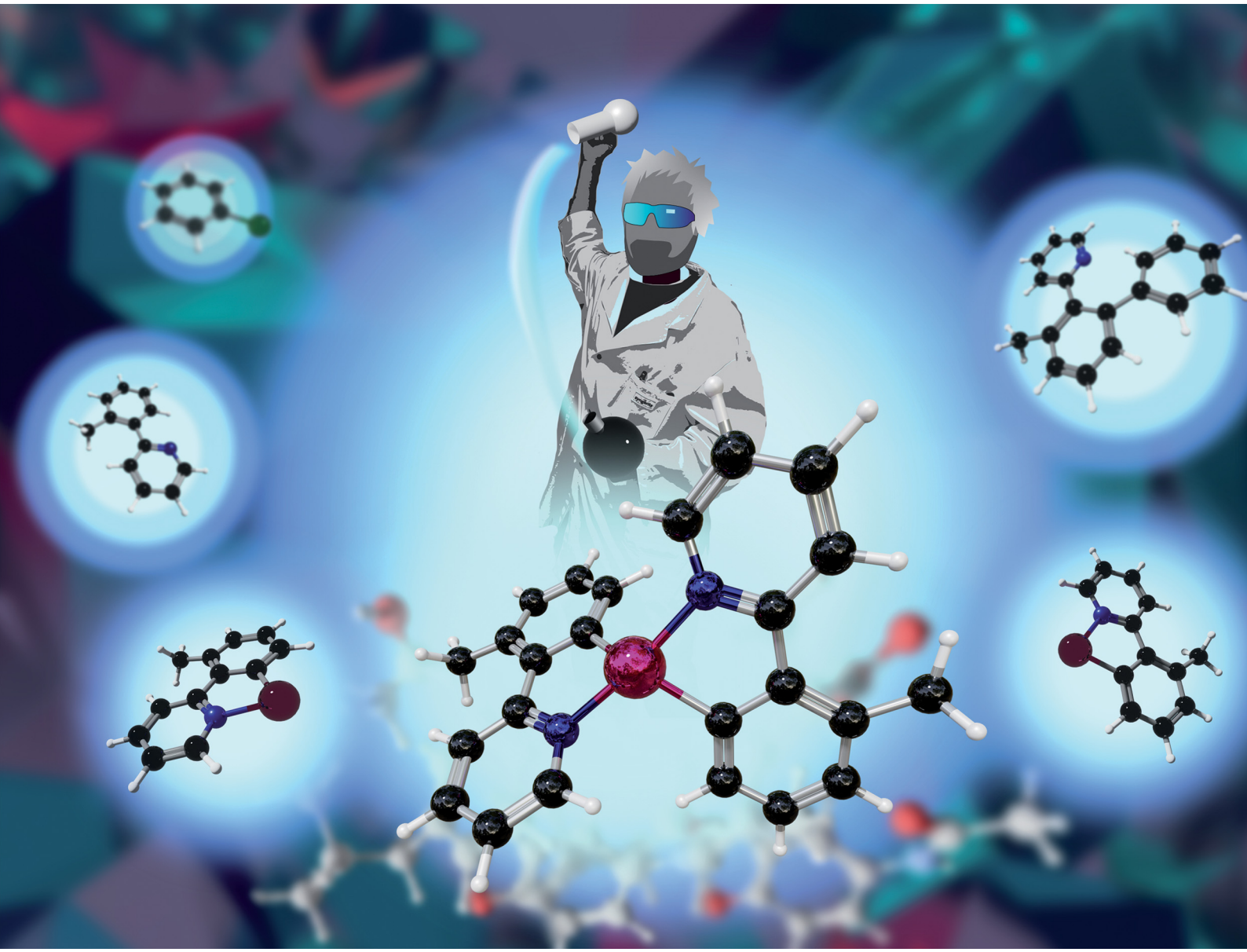

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HIGHLIGHT

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Cyclometallated complexes as catalysts for C–H activation and functionalization

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The development of novel catalysts for C–H activation reactions with increased reactivity and improved selectivities has been attracting significant interest over the last two decades. More recently, promising results have been developed using tridentate pincer ligands, which form a stable C–M bond. Furthermore, based on mechanistic studies, the unique catalytic role of some metallacyclic intermediate species has been revealed. These experimental observations have subsequently translated into the rational design of advanced C–H activation catalysts in both Ru- and Ir-based systems. Recent breakthroughs in the field of C–H activation catalysed by metallacyclic intermediates are thus discussed.

Introduction

Despite the fact that the pioneering observation of a metal-catalyzed C–H activation reaction preceded even the ground-breaking discovery of palladium catalyzed-cross couplings[1] the field remains, after almost four decades, at the forefront of modern organic chemistry (Fig. 1). For decades, the gap between organometallic chemists exploring metallacyclic complexes[2] and synthetic chemists seeking new methodologies for the efficient synthesis of complex molecules was significant.

In consequence, the emergence of catalytic C–H activation-type process in the development of synthetic reactions, occurring *via* the generation of metallacyclic intermediates and their subsequent functionalization, began to intensify only around the 2010s.[3] Today, thanks to the rapid development of this field, C–H activation is a well-established tool commonly used by organic chemists in both academia and industry.[4] Current C–H activation protocols allow for various bond-forming events[5] using an array of metals such as palladium, rhodium, ruthenium, iridium and recently more sustainable 3d-metals.[6] Despite this, the search for more potent catalytic systems is a continuous challenge. In addition, the expanding comprehension and advanced mechanistic studies provide new opportunities to discover and rationally design new catalytic systems. These in turn can promote increasingly challenging or even unprecedented highly selective C–H activation protocols.

In this context, several research groups have revealed the unexpected role of cyclometallated species as catalytically active metal complexes. In this highlight, the discovery of metallacycles as C–H activation catalysts is described and the major advances in this field are discussed to shed light on the unexpected behavior and properties of such species.

Pincer complexes with a key C–M bond

Pincer complexes are an important class of catalysts with various applications in numerous catalytic transformations, including cross-couplings, aldol and Michael reactions, allylations, *etc.*[7] Among the different classes of pincer complexes, donor-carbon-donor structures bearing a C–M bond as the central linkage are particularly important.[8] Due to the high stability of such coordination modes and the electron-donating character of the formally anionic carbon coordinated to the metal, oxidation of the metal center is facilitated. Such catalysts are ideally prepared *via* a C–H activation step, through direct metallation of the ligand by the metal precursor. Such a C–H activation protocol can thus be successfully applied for the synthesis of an array of metal complexes, including Pd, Ni, Co, Ir, Ru, and others.[9] More recently, the catalytic reactivity of such metallacyclic complexes has been evaluated in C–H functionalization reactions. The pioneering example with NCN-Pd **1** was reported already in 2010 by Szabó, who discovered the unique reactivity of such a complex in C–H borylation of alkenes[10] and allylic moieties (Scheme 1a).[11] The catalytic activity of this complex and the selectivity achieved while using allylic substrates probably arises from the easy oxidation of Pd from Pd(II) to Pd(IV), either using hypervalent iodine species, NFSI, or F-TEDA-BF_4 and stabilization of the subsequently generated high-oxidation-state intermediate. This initial oxidation is essential as it modifies the geometry of the NCN–Pd complex from square planar to octahedral thus generating the vacant

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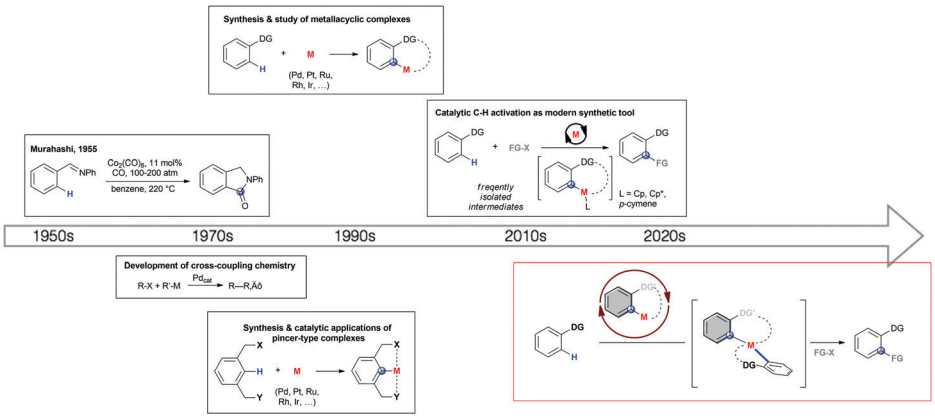
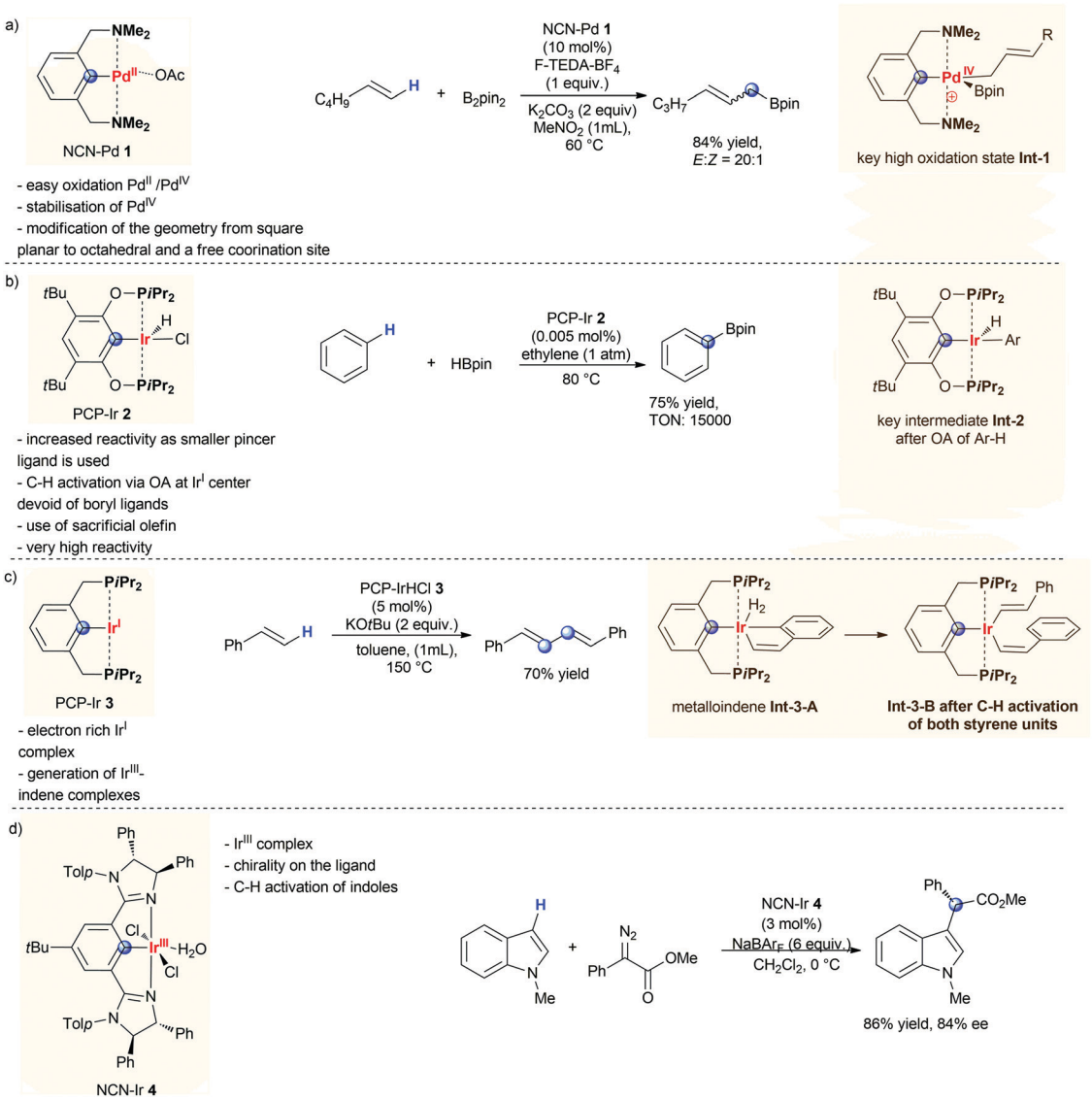


Fig. 1 A short timeline of the development of the catalytic C–H activation *vs.* exploration of the metallacyclic complexes.



Scheme 1

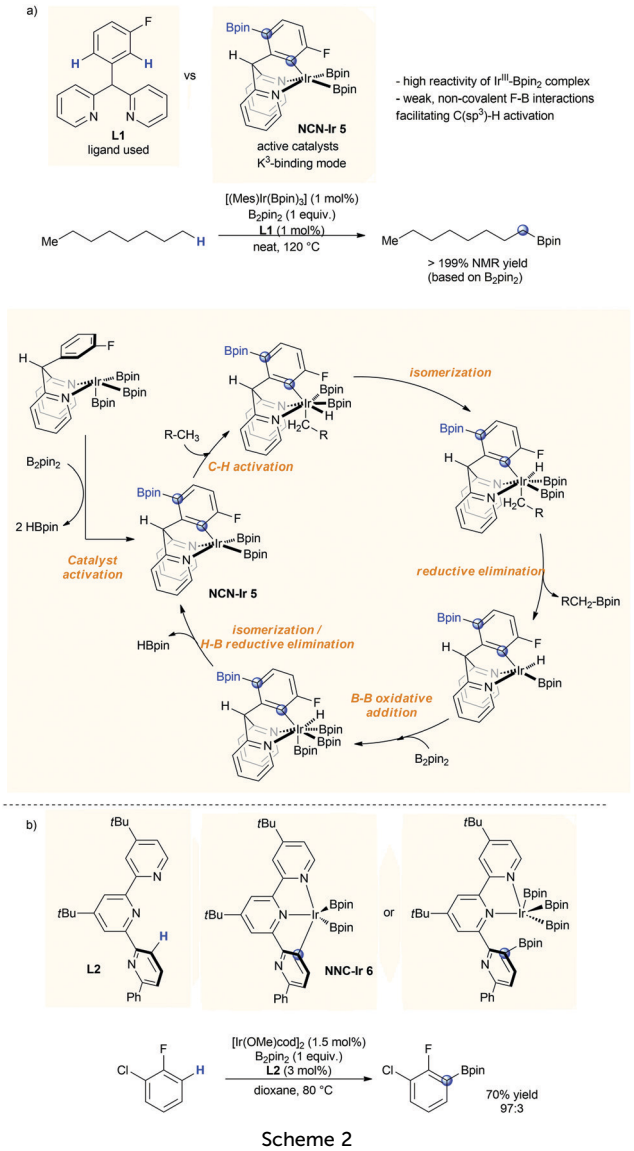
coordination site required for the C–H activation step. The resulting Pd(II)/Pd(IV) catalytic cycle proceeds smoothly and selectively, under surprisingly mild reaction conditions (20–60 °C).

Ozerov further highlighted the great potential of iridium pincer complexes in C–H activation a few years later (Scheme 1b).[12] The Ir–POCOP complex **2** turned out to be a powerful direct borylation catalyst, allowing C(sp^2)–B coupling with TON number up to 10^4. This high catalytic activity arises from the unique reactivity of the pincer ligand. Contrary to the well-known Ir-catalyzed C–H borylation occurring *via* 16-electron triboryl Ir(III)-intermediate,[13] neutral three-coordinate (POCOP)–Ir(I) complex promotes the C–H activation step *via* oxidative addition. Further studies revealed that this reactivity is limited to the pincer complex with a central aryl site, clearly highlighting a unique effectiveness of the metallacyclic species. The natural, sterically-controlled regioselectivity of this C–H borylation provides the mono-borylated arenes as a mixture of *meta*- and *para*-substituted products.[14] However, changing the metal to ruthenium, the same ligand system – POCOP–Ru(I) has been used for directed C(sp^3)–H borylation of amides and esters. Although the reactions required elevated temperature (80–120 °C) and neat conditions, the ligand system demonstrated high regioselectivity even in the presence of sterically unhindered C(sp^2)–H bonds.[15]

Goldman and Jones disclosed a mechanistically quite similar application of the Ir–PCP complex in dehydrogenative C–C coupling between vinyl substrates (Scheme 1c).[16] Based on in-depth mechanistic studies and in accordance with the previous study of Ozerov,[12b] neutral PCP–Ir(I) complex was found to be catalytically active in first the double vinylic C–H activation step leading to a formation of Ir(III)–H intermediate. This higher oxidation state catalyst undergoes intramolecular *ortho*-C_{Ar}–H activation delivering the metalloindene accompanied by H_2 release, consumed by sacrificial styrenes. The activated Ir(III) complex may thus promote second vinylic addition, delivering the desired C–C coupling product after the reductive elimination.

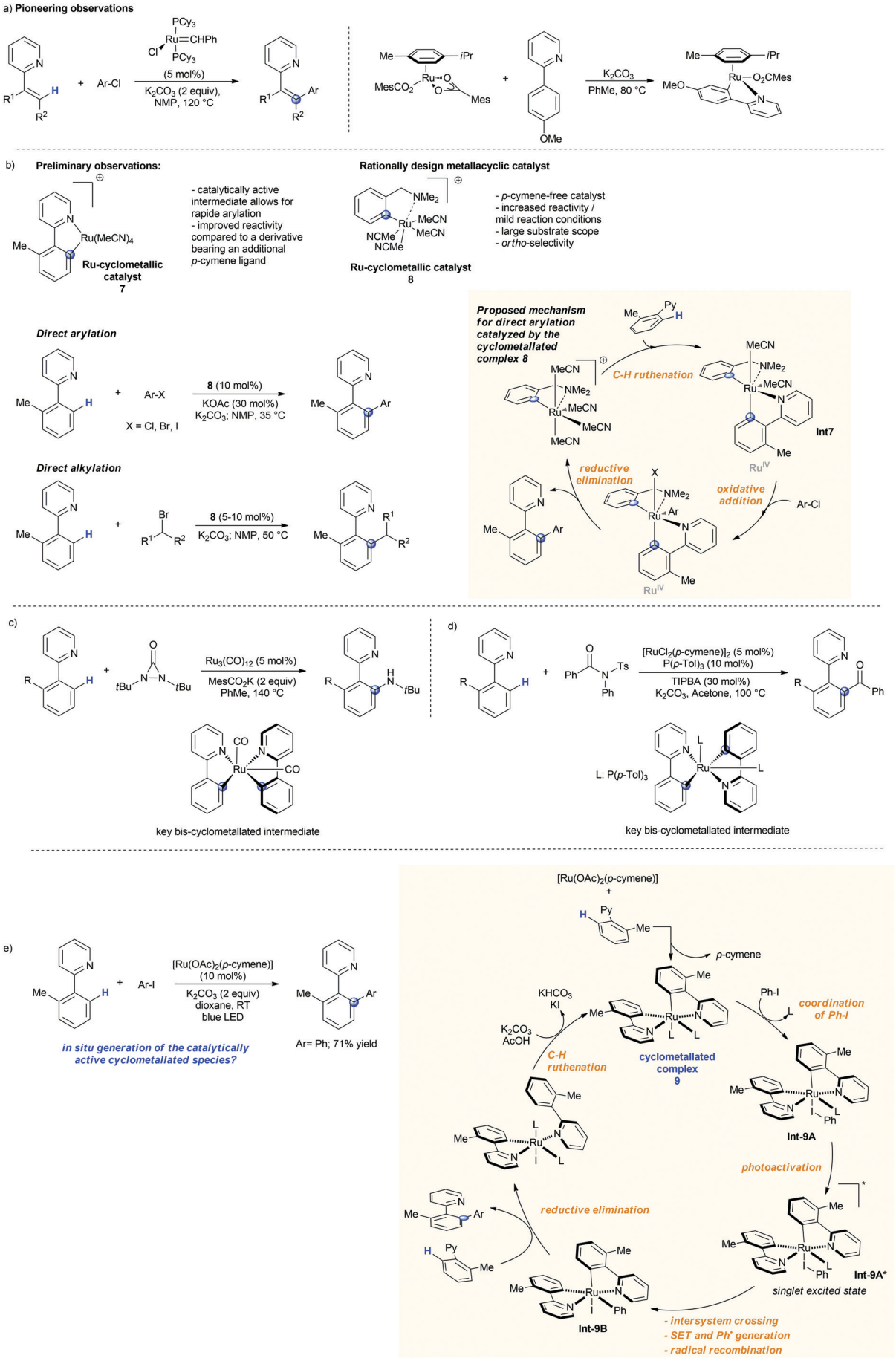
In addition to PCP–Ir complexes, significant attention has been focused on NCN-type complexes, with their pioneering applications in alkane dehydrogenation implying the C–H activation step.[17] Modification of the coordination nature of the pincer ligands strongly impacts the catalytic activity of the Ir-complex. Unlike with PCP ligands, the higher oxidation state Ir(III)–NCN complex is the catalytically active form for the C(sp^3)–H activation. The numerous examples of chiral NCN ligands used for different transition metal catalyzed reactions served as basis for the preparation of chiral Ir(III)–NCN complexes capable of efficient and stereoselective CH-functionalization of ethers[18] and methylindoles (Scheme 1d).[19]

In 2020, the use of tridentate NCN ligands' for Ir-catalyzed direct borylation has been viewed from a different perspective. Schley and his coworkers aimed to design a NCN-ligand able to coordinate in rather facial κ^3 mode, with a possibility of projecting C-donor out of the N–Ir–N plane (Scheme 2).[20] Dipyridylarylmethane derivatives were thus designed as ligands, and superior efficacy of the *meta*-fluorinated **L1** was observed. The **L1** ligand showed exceptionally high reactivity in C(sp^3)–H



Scheme 2

borylation of unactivated alkanes under neat conditions. Authors also observed the incorporation of both Bpin-units from the B_2pin_2 coupling partner. The new catalytic system allows for the use of cyclohexane as an external solvent that drastically reduces the excess of the aliphatic substrate. Although the new ligand **L1** was twice as reactive compared to the benchmark Me_4Phen ligand, the exact mode of action for this catalytic system remained unclear. To answer this question, the group of Huang has initiated intensive, DFT-based mechanistic studies.[21] It was discovered that the initial step of this catalytic reaction involved catalyst activation. First, the ligand undergoes two-fold C–H activation and borylation of the fluorinated-aromatic ring to form the catalytically active **NCN-Ir5**. The superior reactivity of the cyclometallated Ir(III) diboryl complex could thus be attributed to two effects: (1) the F-substituent facilitates the oxidative addition to the C(sp^3)–H bond and the rate-determining isomerization due to non-covalent F–B interactions and (2) the weaker



Scheme 3

trans influence of the cyclometallated phenyl ring compared to the Bpin group present in $Me_4PhenIr(Bpin)_3$-type complexes makes the oxidative C(sp^3)–H addition much more favorable. Based on these investigations, a detailed mechanistic cycle was proposed, involving the key steps: (1) catalyst activation, (2) C–H oxidative addition, (3) isomerization, (4) C–B reductive elimination and (5) catalyst regeneration.

Very recently, Ilies employed a terpyridine derivative as a ligand for Ir-catalyzed *ortho*-borylation of fluoroarenes (Scheme 2b).[22] Ligand studies revealed that the C2-substituent on the peripheral pyridine ring and the *para-tert*-butyl group on the central pyridine ring were crucial. It was therefore postulated that NNC-type metallacyclic intermediate is the catalytically active species. However, as partial ligand-borylation was observed, the exact nature of the catalytically active species remains uncertain.

When substrate becomes a ligand

The chemistry of metallacyclic species and their synthesis has fascinated the scientific community as early as the 70s. Therefore, the early examples of the C–H activation were marked by the design of stoichiometric reactions generating metallacyclic species from simple aromatic amines, amides, and heteroarylarenes. Over the following decades, the scientific community has learned how to functionalize such metallacyclic intermediates, and how to develop the corresponding catalytic process. In the ''classical'' catalytic cycle, the metallacyclic intermediate is formed transiently and the metal is released at the end to restart a new process. Within the development of such reactions, the mechanistic efforts frequently resulted in the isolation of the metallacyclic intermediates and their catalytic activity was often observed. Initial reports showcased that the metallacyclic intermediates can be functionalized and the product release translate in a re-generation of a metallic species bearing strongly binding ligands, such as Cp* in case of Rh and Ir species or *p*-cymene in the case of Ru.[23] However, it was difficult to predict if the metallacyclic species may react as the active catalyst for the second C–H insertion event.

(*p*-Cymene)Ru-complex is one of the central precatalysts in the field of C–H activation. The corresponding applications have expanded over the last 15 years,[24] allowing for a variety of direct C–C and C–X bond formation processes. However, despite the exceptional reactivity of (*p*-cymene)Ru-complex, preliminary reports as early as 2007 revealed that *p*-cymene free Ru-species are also competent C–H activation catalysts.[25] Notably, in 2010 Ackermann *et al.* managed to isolate a cyclometallated Ru-complex as an active intermediate from direct C–H arylation of arenes thus clearly illustrating the fascinating and ambiguous nature of such species (Scheme 3a).[23]

In 2018 an in-depth mechanistic studies on direct arylation of phenylpyridine derivatives with aryl (pseudo)halide brought a new perspective and on the nature of the catalytically active Ru-species (Scheme 3b). The previously acknowledged postulate suggested that (*p*-cymene)Ru-species are promoting C–H activation on phenylpyridine, followed by oxidative addition of Ar–I to the metallacyclic intermediate. However, Larrosa discovered that contrary to this, the arylation reaction is in reality poisoned by the presence of *p*-cymene ligand.[26] Instead, a cationic *p*-cymene-free metallacycle complex **7** is smoothly converted into the arylated product, by adding an additional phenylpyridine equivalent. Further studies revealed that the cyclometallated *p*-cymene-free catalyst promoted a second C–H activation step, forming the key bis-cyclometallated intermediate. The oxidative addition of the coupling partner is favored for such an electron-rich bis-cycloruthenated catalyst at temperatures as low as 25 °C, thus allowing the desired arylation to occur under much milder reaction conditions. Based on these mechanistic observations, the cyclometallated, (*p*-cymene)-free catalyst **7** was isolated and characterized. The complex **7** exhibited superior reactivity to the standard (*p*-cymene)Ru-precursor, illustrating the unexpected activation mode *via* the use of a cyclometallated catalyst. However, the use of a cyclometallated catalyst raises a key question of selectivity, when a biscyclometallated intermediate bears two different NC-ligands. To address this point, an alternative NC-ligand, dimethylbenzylamine, was designed. Complex **8** turned out to be a suitable catalyst candidate, suppressing the undesired ''catalyst arylation'' degradation pathway. Selective functionalization of the phenylpyridine substrate was achieved with no formation of the undesired *ortho*-arylated methylbenzylamine-product.

These new types of Ru-catalysts clearly outcompete the classical reactions, promoting the desired C–H activation at temperatures as low as 35 °C. The advantageous features of this catalyst render it appealing for late-stage diversification of a variety of complex, drug-like molecules.

Subsequently, the reactivity of the cyclometallated Ru-complex could further be exploited in *ortho*-directed alkylation using secondary[27] and primary halides (Scheme 3b).[28] In both cases, the electron-rich character of the Ru(II) bis-cyclometallated species renders oxidative addition to the X–C(sp^3) bond feasible. As expected, the directed C(sp^2)–C(sp^3) couplings were productive while using the precatalyst **8**, which *in situ* generated the key biscyclometallated Ru complex. Importantly these alkylation reactions show an alternative regioselectivity compared to the Ru(*p*-cymene)-catalyzed transformations.[29] In the presence of a secondary alkyl halide the key biscyclometallated intermediate is expected to undergo an S_N2-type oxidative addition process, thus clearly differing from the previously known systems implying SET or S_EAr-type mechanisms.

Following these seminal studies by Larrosa, other groups have also investigated this type of catalytically active species. Liang postulated that cyclometallated-Ru complex is the catalytically active species in the *ortho*-C–H amination of a range of heteroaryl arenes using di-*tert*-butyldiaziridinone and $Ru_3(CO)_{12}$ precatalyst (Scheme 3c).[30] Zhang and Bao focused on direct acylation reaction occurring *via* C–H and C–N activation.[31] Their mechanistic studies suggest that if Ru(*p*-cymene) dicarboxylate precatalyst is used the initial C–H activation leads to a metallacyclic intermediate. This is followed by decoordination of the 6-π-ligand in the second

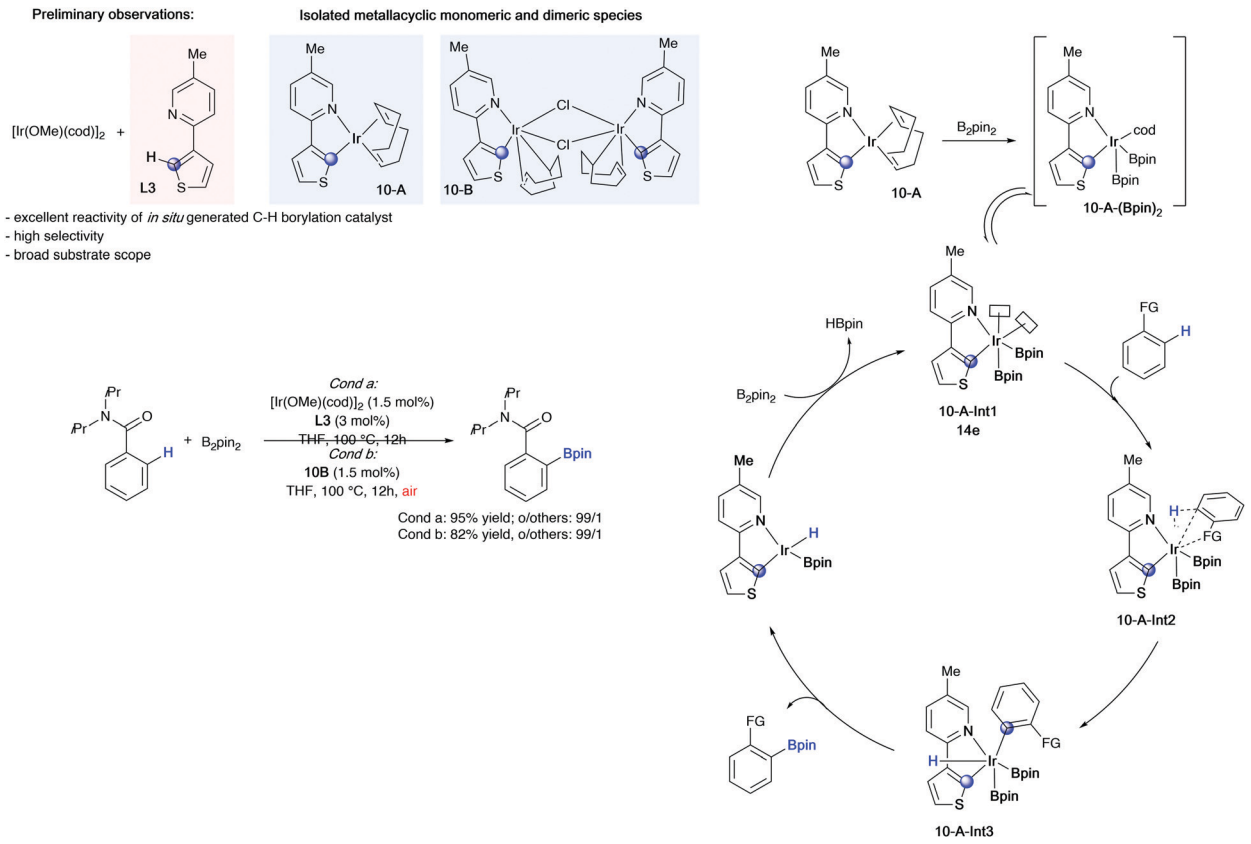
C–H activation event, furnishing the electron-rich bis-cyclometallated species (Scheme 3d). The formed electron-rich complex allows for oxidative addition into the C–N bond of the amide substrate, followed by reductive elimination delivering the expected functionalized compound. However, contrary to the Larrosa's catalytic systems for direct alkylation and arylation, this acylation reaction required a high reaction temperature (100–120 °C).

The group of Ackermann further elucidated the unique potential of Ru-metallacyclic species (Scheme 3e).[32] In 2020 they discovered that biscyclometallated Ru-species **9** are the catalytically active species in the C–H activation and they are prone to absorb light thus triggering a photocatalytic reaction. Based on this discovery, a unique, mild, and general catalytic system was designed for a photomediated but external photocatalyst-free direct arylation of arenes, using aryliodides as the coupling partners. Contrary to the Larrosa work, this *ortho*-selective reaction occurs *via* a radical-type process. Initially the bis-cyclometallated species is generated *via* double C–H activation and decoordination of the *p*-cymene ligand, followed by the coordination of the iodo–arene coupling partner (**Int-9A**).

The intermediate **Int-9A** efficiently absorbs blue light to form an excited singlet state (**Int-9A***) which is rapidly converted *via* intersystem crossing into long-lived triplet excited state. Inner-sphere electron-transfer results in the generation of key Ru(III)-species and an aryl radical, that readily recombine towards the expected Ru(IV)-intermediate **Int-9B**. Reductive elimination from **Int-9B** delivers the functionalized product and regenerates the catalytically active Ru-bis-cyclometallated catalysts. It is important to highlight here that this radical process also differs from the largely described in the literature Ru-catalyzed *meta*-selective alkylations that take place *via* aryl-radical/carbocation intermediates.[33,34]

NC cyclometallated catalysts for C–H activation: not only Ru

While regarding the unique potential of the cycloruthenated species in direct functionalization reactions, it is not surprising that generalization of this concept towards other transition metals appears tempting. The first step towards this goal was recently done by Chattopadhyay, who has established a new and particularly general protocol for the direct borylation of a large variety of substrates (Scheme 4).[35] While searching for a general catalytic system promoting novel C–B couplings, the authors evaluated a large panel of ligands, rapidly disclosing the superior reactivity of phenylpyridine type scaffold prompt to act as a bicoordinating NC ligand. The catalytic reactivity could be further improved by facilitating the cyclometallation event, by means of decreasing the pK_a of the C–H bond. Following this hypothesis, optimal efficiency was achieved while using pyridinethiophene (**L3**) and pyridinefurane type



Scheme 4

ligands. The *in situ* generated Ir-complexes using $[Ir(cod)OMe]_2$ as the precatalyst, allowed for unprecedently general direct borylation protocol, compatible with a variety of functionalized aromatics bearing different DG, and C(sp^3)–H bonds adjacent to the N-atom. However, for heteroaryl compounds the effect of different DG was less significant. Depending on the used Ir precatalyst, the cyclometallated Ir monomeric **10A** and dimeric complexes **10B** could be formed under modified reaction conditions. Remarkably, the dimeric Ir(III) cyclometallated complex **10B** turned out to be air-stable, efficiently promoting the desired reaction under air atmosphere. The authors suggest that the monomeric 16-electron diborylated **10A-(Bpin)$_2$** is operating in a catalytic cycle. First the 14-electron active species (**10A-Int1**) is formed *via* the loss of the COD ligand. The formed complex bears two free coordination sites required to accommodate the substrate *via* C–H activation, furnishing the Ir(V) intermediate. Reductive elimination and activation of B_2pin_2 closes the catalytic cycle.

Finally, an additional example of C–H bond oxidation of toluene was reported in 2017, using well-defined metallacyclic complexes, however a radical mechanism is expected be operative in this case.[36]

Conclusions

Over the last few years, the field of C–H activation has witnessed a real advance enabled by the discovery of the unique role of metallacyclic species. Previously such motifs were only extensively studied by coordination chemists and frequently proposed as the key intermediates within the catalytic C–H activation. Now the metallacycles have revealed to be particularly active catalytic species allowing for more efficient, milder, and more selective C–H activation protocols. Following these discoveries, the design of Ir- and Ru-based stable metallacyclic catalysts, bearing a ''non functionalizable'' strongly coordinated XC ligand is an attractive new research direction. Interesting perspective also lies in the recent isolation and characterization of different metallacyclic intermediates based on more abundant and sustainable 3d-metals, such as Co and Ni. This strongly suggests that bis-cyclometallated species may also be key species in the corresponding C–H activation reactions.[37] The recent years will thus certainly be marked by the development of new metallacyclic catalytic systems for advanced direct functionalization reactions. The potential of the stable and electron-rich cyclometallated catalysts goes far beyond the C–H activation and such modern complexes have clearly opened new perspectives in others fields of homogeneous catalysis for example hydrosilylations,[38] asymmetric hydrogenations[39] and imines synthesis[40] without forgetting the key role of metallacyclic species in photoredox catalysis.[41]

Author contributions

J. M. Z., T. S. and J. W.-D.: writing of the original draft & revisions.

Conflicts of interest

There are no conflicts to declare.

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