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Recent advances in Manganese-catalysed C-H activation: Scope and mechanism

Rafael Cano, Katrina Mackey, and Gerard P. McGlacken

As a synthetic methodology, C-H activation represents a complimentary protocol to traditional cross-couplings such as the Suzuki-Miyaura and Stille reactions, by avoiding the extra synthetic steps required to install activating groups. C-H activation also often avoids the production of waste associated with B, Sn, halide etc. Pd-catalysed transformations have been most prominent in the C-H activation realm. However, as a society we are over-reliant on transitional metals, cost is increasing, and the accessible supply is dwindling. One potential solution is to develop chemistry using Earth Abundant Metals (EAMs). Manganese (Mn), in particular, demonstrates great promise. Since the publication of an excellent review by Ackermann in 2016 [ACS Catal. 2016, 6, 3743-3652], there has been a flurry of reports on Mn-catalysed C-H activation. We report here an overview of approximately 30 new papers, which include a number of notable advances since April 2016.

1 Introduction

As a society, we are over-reliant on precious metals. Palladium, platinum, rhodium, ruthenium and iridium have been classed as EU Critical Raw Materials as a result of limited production capacities, and their key applications as catalytic converters, and in the pharmaceutical and energy sectors. Within the pharmaceutical industry, palladium, without doubt, plays the most prominent role among the precious metals. However, Pd is rare in the Earth’s crust (0.89 ppm) and its cost is steadily increasing. Clearly, there is an urgent need to alleviate the worldwide reliance on platinum group metals, and palladium in particular.

One potential solution is to develop chemistry using Earth Abundant Metals (EAM). Use of 3d transition metals is commonly reported now, with complexes derived from iron and nickel (and cobalt to a certain extent) proving the most useful. However, manganese-based systems, in particular, have demonstrated great promise. Firstly, manganese is the twelfth most abundant element in the Earth’s crust and the third most abundant transition metal after iron and titanium. The low toxicity and low cost of manganese render it a particularly attractive alternative to the typically used transition metal catalysts. Manganese is found as an essential trace element for life on Earth. For instance, several manganese containing enzymes are essential for metabolizing carbohydrates, cholesterol, and amino acids in the human body. Overall it demonstrates a far lower health and environmental impact than platinum group metals.

Rafael Cano obtained his BSc and PhD at the University of Alicante. In 2013, he accepted a post-doctoral position with the McGlacken group at University College Cork. While there, he undertook research secondments at Merck (Ireland) and at the University of Oxford (UK) with Prof. Michael C. Willis. His research is focused on heterogeneous catalysis and asymmetric synthesis.

Katrina Mackey obtained her BSc in Chemistry with Forensic Science at University College Cork, Ireland. In 2014, she began her PhD in the McGlacken group at University College Cork. Her research is focused on using C-H activation strategies toward the synthesis of biologically important heterocycles.

Gerard McGlacken obtained his PhD at the National University of Ireland, Galway. He then moved to the University of York to work on organometallic transformations with Prof. Ian J. S. Fairlamb. A year later, he took up a Molecular Design and Synthesis Post-Doctoral Fellowship at Florida State University working with Prof. Robert Holton. He obtained a Lectureship position at University College Cork in 2007.
C-H activation represents a challenging, yet highly rewarding methodology, in modern synthetic chemistry (Fig. 1). Traditional methods (Suzuki-Miyaura, Stille, Negishi etc) for the functionalisation of inert C-H bonds requires pre-activation of both coupling partners as halides, pseudohalides, boronic acids, stannanes, organozincs, etc. This often lengthens the synthetic route and generates waste derived from the activating groups. A key achievement in the last decade is the development of C-H activation protocols, which can mitigate some of these issues (Fig. 1).

![Fig. 1](Image)

**Fig. 1** (A) Traditional functional group transformation and (B) C-H bond activation methodology.

The activation of inert C-H bonds has been recognized as an important synthetic tool in organic synthesis, with broad ranging applications in a number of different fields including medicinal chemistry, natural product synthesis and material sciences. Furthermore, the ability to selectively target a number of different C-H bonds in a complex substrate, permits direct access to multiple analogues from a common structural precursor. In particular, the advantages of modern C-H activation methods to synthesise aromatic and heteroaromatic compounds via C-H activation are among the published ‘Wanted List’ of top pharmaceutical companies. Undoubtedly the C-H activation field has been dominated by catalysts based on noble transition metals such as ruthenium, rhodium, palladium, iridium or platinum. Using these 4d and 5d transition metals, some strides have been made towards more sustainable C-H activation modes, for example, using mild conditions or heterogeneous catalysts. In the last few years, new catalytic systems based on abundant and inexpensive EAMs such as magnesium, calcium, manganese, iron, copper and zinc have been reported. Among these, manganese has attracted special attention due to its reactivity and potential versatility.

In general, first row transition metal based catalysts usually display different and complementary catalytic activities to second and third row transition metals. Manganese exhibits the widest range of oxidation states of any of the first row d-block metals (-3 to +7) and has the ability to form compounds with a coordination number of up to 7. Many of the difficulties surrounding the use of manganese in classical organometallic reactions stems from the lack of well-characterised examples of organomanganese complexes in oxidation states other than +1. Although manganese is most frequently encountered in the +2 state, the majority of its organometallic chemistry concerns the univalent state. These Mn(I) compounds exhibit almost exclusively low-spin d⁰ configurations and typically feature very strong crystal field ligands such as carbonyl. This is not surprising as, in general, transition metal complexes in low oxidation states are almost always stabilized by π-acceptor ligands such as CO, NO or PR₃. However, only a limited number of manganese catalysed C-H bond activation protocols have been reported to operate by an organometallic mode of action and they normally utilise the Mn(I) catalysts: Mn(CO)Br and Mn₂(CO)₁₀.

On the other hand, manganese catalysed C-H oxygenations, nitrogenations and halogenations catalysed by high valent manganese species, proceeding via a radical mechanism have been well developed. These methods lead to functionalisation at the weakest C-H bond in the substrates, typically at the benzylic position. Recently however, manganese catalysed organometallic C-H functionalisation at thermodynamically more stable aryl or alkenyl C-H bonds has gained considerable momentum and some progress has been made prior to this review. Since the seminal report by Stone, Bruce and Co-workers, and stoichiometric transformations by Liebeskind, Nicholson and Main, and Woodgate, key contributions involving catalysis, from the groups of Kuninobu/Takai, Wang, Ackermann, and others have changed the landscape of Mn-catalysis. Various manganese catalysed C-H allylations, C-H alkynylations, C-H hydroarylations and C-H halogenations have been successfully achieved. Several arenes and heteroarenes have been coupled with aldehydes, isocyanates, nitriles, alklenes, terminal and internal alkynes and oxiranes (Fig. 2). In all these examples the action of a directing group such as a nitrogen-containing heterocycle or an imine group is necessary. Preliminary mechanistic studies revealed a isohypsic mode of action frequently involving base assisted cyclometallation and a migratory insertion step.

![Fig. 2](Image)

**Fig. 2** C-C bonds formed by Mn-catalysed C-H activations.
Since the publication of an excellent review on Mn mediated C-H activation by Ackermann in 2016, reports on Mn-catalysed C-H activation have emerged steadily. We report here an overview of 35 papers since April 2016. There have been notable advances during the last couple of years, especially in the scope of transformations available and the mechanistic insights garnered.

### 2 Mn-catalysed C-H activations by coordination-directed metallation

#### C-H Activation of Arenes

A Mn-catalysed C-H activation for the allylation of arenes was reported by Ackermann. Imines were reacted with different substituted electrophiles (Fig. 3). The imine acted as a crucial directing group for Mn, and was easily removed under acidic conditions to furnish the corresponding ketones. In this example, the two most widely employed manganese complexes \([\text{Mn}_2(\text{CO})_{10}]\) and \([\text{MnBr}(\text{CO})_5]\) showed excellent activity, as well as excellent chemoselectivity, tolerating a wide number of functional groups (amino, halogen and cyano etc). Examples using substrates with substituents at the meta position gave further information about the reaction mechanism and provided evidence that, in general, the regioselectivity was governed by steric interactions.

![Fig. 3 Mn-catalysed C-H allylation of imines.](image)

However, in cases where substituents possessed a directing-group (e.g. piperonyl), only one regioisomer was produced (Fig. 4). High levels of stereocontrol were achieved with substituted allylic carbonates, and the E-isomer was formed predominantly. No double-bond isomerisation to the thermodynamically more stable styrene derivatives was observed in any case.

![Fig. 4 Regio- and stereocontrol of the C-H allylation of imines (only major regioisomer shown).](image)

This methodology was not limited to arenes. Other biologically relevant heterocycles also proved suitable for Mn-catalysed C-H allylation under similar reaction conditions. In these cases, the introduction of the 2-pyridyl moiety as a directing-group was necessary. A formyl group remained untouched during the process supporting the involvement of organomanganese rather than manganese hydride intermediates.

The authors performed a series of reactions with isotopically labelled substrates which provided some information on the mode of action of the catalyst. Kinetic isotope effects (KIE) determined by intermolecular and intramolecular competition experiments were indicative of a fast C-H manganesation process (Fig. 5). Additional competition experiments and a manganese catalysed H-D exchange experiment both supported a base-assisted electrophilic (BIES) type of C-H activation.

![Fig. 5 (a) Intra- and (b) intermolecular KIE experiments.](image)

Thus a mode of action involving an organometallic Mn-catalysed substitutive C-H activation by redox neutral carboxylate assistance was proposed (Fig. 6). However, an alternative activation of the allyl carbonate by an oxidative addition is not discarded. The cycle is initiated by the coordination of the imine to the Mn-complex, followed by the
C-H activation. Then carboxylate coordination and CO insertion gave a 7-membered intermediate.

**Fig. 6** Proposed mechanism for the Mn-catalysed C-H allylation of arenes.

A β-hydride elimination then gives the corresponding product, while decarboxylation and salt metathesis regenerates the Mn-complex. Although the dimeric complex \([\text{Mn}_2(\text{CO})_{10}]\) demonstrated considerable catalytic efficiency, the use of NaOAc as a co-catalytic additive improved the results. The C-H alkenylation of aromatic N-H imidates with alkynes has been developed by the Wang group.\(^{39}\) This is a useful strategy, providing access to *ortho*-functionalised aromatic nitriles. Firstly, the cyano group is masked using alcohols in the presence of AcCl to prepare the corresponding benzimidate that will also act as a directing group for the *ortho*-C-H activation. After reaction with the alkynyl, the cyano group is unmasked to reveal the corresponding *ortho*-alkylated nitrile (Fig. 7). Electron-donating and electron-withdrawing groups were allowed on the aromatic ring of the alkyne, and halogens (Cl, Br) which are potentially susceptible to further functionalisation, were well tolerated. The yields (24-40%) were notably decreased when internal alkynes were used. A high number of functionalities were also tolerated on the aromatic ring of the imidate. When substituents at the *meta*-position were used, the reaction proceeded at the less sterically hindered position preferentially (10:1 for Me, 100:1 for CF\(_3\)) except in the case of the piperonitrile derivative, which gave alkenylation at the more sterically hindered position.

![Proposed mechanism for the Mn-catalysed C-H allylation of arenes](image)

**Fig. 7** Mn-catalysed *ortho*-C-H alkenylation of aromatic imidates with alkynes.

The proposed mechanism of the reaction starts with the NaOPiv-assisted cyclomanganation of the benzimidate to give I (Fig. 8), which then undergoes an alkynyl-insertion of the Mn-C bond affording the seven-membered manganacycle II via the alkynyl–Mn complex III. Two pathways are then proposed depending on whether the alkynyl is terminal or internal. For terminal alkynes (path A), a second alkynyl is coordinated giving IV, and then an intramolecular H-shift leads to the formation of alkynyl manganese V. A ligand exchange takes place between V and the benzimidate resulting in the alkenylated benzimidate. Subsequent complexation of substrates and C-H activation of the benzimidate in the presence of NaOPiv regenerates II.

![Proposed mechanism for the Mn-catalysed C-H alkenylation of imidates](image)

The bicyclic annulations of imines and α,β-unsaturated esters via Mn-catalysed C-H activation has also been reported.\(^{40}\) Based on previous work carried out by Ackermann on the Mn-catalysed synthesis of cis-β-amino acid esters from ketimines and α,β-unsaturated esters,\(^{36a}\) they proposed a new methodology that combines Mn and Zn catalysis to afford fused β-lactams (Fig. 9). The reaction showed a high functional group tolerance on the ketimine ring. Moreover, it was possible to use aldimines under the same conditions (CuBr was used as additive in this case). Substitution near the carbonyl on the acrylates had a strong influence, and a decreased yield was observed.
Based on several experiments performed, a bimetallic catalytic cycle was proposed by the authors (Fig. 10). Firstly [MnBr(CO)₅] reacts with Me₂Zn to give [MnMe(CO)₅], which undergoes C-H metallation of the ketimine to afford I (which was possible to isolate). Mn-enolate II was formed by insertion of methyl acrylate to the C-Mn bond of I. Subsequent intramolecular nucleophilic attack gives intermediate III. The metathesis of the ligand with Me₂Zn and complexation with ketimine furnished IV and Zn-I. C-H activation in IV regenerates I and a second intramolecular nucleophilic cyclisation of Zn-I formed the corresponding β-lactam.

A further example of bimetallic catalysis was reported by Wang and co-workers. Imines and allenes were reacted in an Mn- and Ag-catalysed process involving a C-H allenylation, followed by a Povarov cyclisation, in one pot (Fig. 11). During the process, three new C-C bonds are formed and two quaternary carbons are generated. Substrates with substituents at the meta-position reacted predominantly at the more sterically congested position, providing evidence of the presence of a secondary directing effect. Trialkyl, diaryl or tetrasubstituted allenes failed in this reaction and monosubstituted allenes gave only the C-H allylation product.

A related methodology was described by Ackermann and co-workers. Similar products could be prepared using methylenecyclopropanes instead of allenes, by using a combination of Mn- and Zn-catalysis (Fig. 13).
Manolikakes’ group reported a Mn(OAc)₃-promoted cross-dehydrogenative coupling of sodium and lithium sulfinates with 1,4-dimethoxybenzenes (Fig. 14). Surprisingly the reaction failed with other electron-rich arenes (anisole, 1,2- or 1,3-dimethoxybenzenes). The solvent and Mn(OAc)₃ were crucial for the success of this transformation, but the exact role of both species remains unclear at this stage.

Alkylations with β-hydrogen-containing alkyl halides were also accomplished via Mn-catalysed C-H activation (Fig. 15). In this work MnCl₂ was used as the catalyst in the absence of Zn or phosphines, to achieve the alkylation of benzamides. Substitution of the amide with the removable triazolylmethyl (TAM) group was mandatory. The use of tertiary amides was unsuccessful.

A new strategy to prepare isoquinolines and isoquinolones has been reported by the Glorius group. The ever-present limitation of controlling stereoselectivity in C-H activation with unsymmetrical alkynes, is solved here, with the introduction of a traceless directing group. The introduction of this directing group (which serves as both chelator and internal oxidant), offers control of the regioselectivity. Aryl ketimines and arylimidates could be reacted with propargylic carbonates affording the corresponding isoquinolines (Fig. 16a). Other heterocycles such as thiophene and benzothiophene-based moieties were also utilised. The utility of this methodology was highlighted by the preparation of an array of isoquinolines with switchable regioselectivity. These substrates had not previously been successfully prepared as single isomer using C-H activation methods (Fig. 16b).

The reaction probably commences with base assisted cyclomanganation of the imine forming a 5-membered manganacycle (Fig. 17). Coordination of the carbonyl oxygen of the carbonate takes place to form II, which is followed by regioselective insertion of the alkyne to deliver III. Subsequent selective β-oxygen elimination affords the allene intermediate IV and regenerates the active [Mn] complex. Finally, the isoquinoline is obtained after intramolecular cyclisation of IV.
A very interesting reaction has been described by Wang and co-workers. The manganese-catalysed addition of ketones to imines is accomplished in this notable work by the combination of Mn- and Zn-catalysis (Fig. 19a). Remarkably, the expected reactivity of C-H bonds α to the carbonyl is suppressed with the aid of manganese, at the same time that the less reactive C-H bond on the aromatic ring is activated. Moreover, cyclised exo-olefinic isoindoline and three-component methylated isoindoline derivatives can be selectively obtained by slight modification of the reaction conditions (Fig 19b).

The mechanism proposed by the authors starts with the formation of [MnMe(CO)₅] from [MnBr(CO)₅] and Me₂Zn (Fig. 20). Reaction with the ketone gives the five-membered manganacycle I that further reacts with the imine to afford II. Transmetallation of II with Me₂Zn affords intermediate III, which undergoes a ligand exchange with the ketone producing IV and Zn-I. Then an intermolecular C-H activation takes place with IV, regenerating I and releasing methane. Hydrolysis of Zn-I yields the corresponding arylated imine. Alternatively, Zn-I can also undergo an intramolecular cyclisation to yield intermediate Zn-II. Finally, an elimination of zinc salt gives the exo-olefinic isoindoline, or an intermolecular nucleophilic substitution with Me₂Zn forms the isoindoline.

The Mn-catalysed directed methylation of alkenes has been reported by Nakamura’s lab using MnCl₂·2LiCl and MeMgBr. 1-Bromo-2-chloroethane was also needed as a mild oxidant. This system is applicable to aromatic, heteroaromatic and olefinic isoindoline and three-component methylated isoquinolines.

**Fig. 17** Proposed mechanism for the Mn-catalysed synthesis of isoquinolines.

**Fig. 18** Mn-catalysed directed methylation of C(sp²)-H bonds.
Recently Bao and co-workers reported the Mn-catalysed C-H cyanation of arenes with \( N \)-cyano-\( N \)-(4-methoxy)phenyl-\( p \)-toluenesulfonamide as cyanating reagent (Fig. 21).\(^\text{48}\)

![Fig. 20](image)

**Fig. 20** Mechanism for the Mn-catalysed addition of ketones to imines.

The proposed mechanism starts with the formation of the manganacycle I (Fig. 22). The coordination of the cyanating reagent facilitated by the presence of an electron-donating group at the para-position gives II. Subsequent insertion of the C\( \equiv \)N into the Mn-C aryl bond generates the seven-membered manganacycle III. The reactive species IV and the cyanated product are formed by rearrangement of III. Finally, ligand exchange yields I to complete the catalytic cycle.

![Fig. 22](image)

**Fig. 22** Proposed mechanism for the cyanation of arenes

C-H Activation of Heteroarenes

Recently, a very interesting study has been reported by Fairlamb and co-workers.\(^\text{49}\) They studied the C-H activation reaction of 2-pyrones with phenylacetylene, and in the process gained some key information on the mechanism of some Mn-catalysed reactions (Fig. 23). They proposed that the 2-pyrone ring system bearing a 2-pyridyl directing group could be an excellent hemilabile ligand for Mn, providing the stabilisation necessary for observation of the key intermediates in this process.

![Fig. 23](image)

**Fig. 23** Study of Mn-catalysed C-H activation of 2-pyrones.

Complex I was obtained in quantitative yield, was fully characterised and its structure was confirmed by single crystal X-ray analysis. UV irradiation and subsequent reaction with phenylacetylene led to the formation of complex II, which was experimentally detected by NMR spectroscopy. Warming of the solution to room temperature led to the formation of III by reductive elimination. Again it was possible for the authors to characterise and confirm by X-ray analysis the formation of this complex. DFT methods were also applied to show the reaction...
pathway that led to the formation of III. When II was allowed to react in neat phenylacetylene, H-transfer was favoured over reductive elimination and product IV was obtained as well as the unexpected products V and VI. All the products were confirmed by X-ray analysis. After demonstrating with clear evidence the key role of 7-membered manganacycles in Mn-catalysed C-H activation processes and the influence of the reaction conditions to favour the formation of different products, the authors showed the influence of the directing group. A small modification of the directing group structure resulted in the formation of a different product (Fig. 24). The introduction of a methoxy group at the pyridyl ring gave the double alkyne insertion product exclusively. This observation was supported by DFT studies, demonstrating the strong influence of the directing group on this process.

Based on preliminary investigations, Ackermann proposed a mechanism initiated by an organometallic C-H metalation leading to complex I (Fig. 26). Next, coordination of the ketone takes place forming complex II and addition to the carbonyl gives the seven-membered manganacycle III. Intermediate III was detected by ESI-MS spectrometry. After a protonative demetallation, the final product was produced and complex I is regenerated. C-H metatation occurring by a metal-assisted σ-bond metathesis by a ligand-to-ligand hydrogen transfer was proposed to explain the selectivity.

Fig. 24 Double alkyne insertion.

Ackermann reported the hydroarylation of carbon-heteroatom multiple bonds using manganese catalysis and without the addition of additives (Fig. 25a). Remarkably [Mn2(CO)10] and [MnBr(CO)5] showed an unprecedented selectivity for the C-2 position of indoles. For comparison, other transition metal-based systems tested gave the C-3 substituted product. In addition, this Mn-based methodology was suitable for the more challenging hydroarylation of ketones and aldehydes. The first C-H functionalisation/addition to imines, was also reported in the same paper (Fig. 25b).

The same group reported the C-H cyanation of heterocycles by means of synergistic heterobimetallic catalysis. Conjunct action of Mn and Zn allowed the cyanation of different heterocycles using N-cyano-N-phenyl-p-toluenesulfonamide, and displayed an excellent tolerance of functional groups (Fig. 27). Pyrroles, thiophenes and even tryptophans were successfully cyanated.

Fig. 25 (a) Mn-catalysed C-H hydroarylation of C=Het; (b) C-H activation with imines.

Fig. 26 Proposed mechanism for the Mn-catalysed hydroarylation of heterocycles.

Fig. 27 (a) Mn-catalysed C-H cyanation of simple indoles; (b) C-H cyanation of other heterocycles.
Ackermann and co-workers also reported the C-H alkylation of indoles and pyrroles in the presence of [MnBr(CO)₅] (Fig. 28). Silly haloalkynes were employed with good results. Moreover, it was possible to extend the methodology to non-activated aryl, alkenyl and alkyl haloalkynes under the same conditions by the addition of BPh₃. As usual in Mn-catalysis the activated aryl, alkenyl and alkyl haloalkynes under the same conditions were also reported.

Moreover, it was possible to extend the methodology to non-activated aryl, alkenyl and alkyl haloalkynes under the same conditions by the addition of BPh₃. As usual in Mn-catalysis the activated aryl, alkenyl and alkyl haloalkynes under the same conditions were also reported. The practical utility of this approach was further demonstrated in this remarkably dense and expansive report, by successful reactions on substrates bearing a fluorescent tag, a complex steroid motif and an enantiomerically pure amino acid. It could also be applied to peptides.

![Fig. 28 Mn-catalysed C-H alkylation.](image)

The first cycle of the mechanism is shown in Fig. 29. Loss of CO occurs, with the base picking up HBr, in an overall fast and facile C-H activation, giving a 5-membered manganacycle I. A migratory insertion of the alkyne takes place to form the 7-membered Mn-complex II. Finally, a β-elimination process yields the desired product and regenerates the active catalyst MnBr(CO)₄. An alternative mechanism involving oxidative addition and reductive elimination could not be ruled out.

![Fig. 29 Proposed mechanism for the Mn-catalysed C-H alkylation.](image)

Other functionalisations have been incorporated into the indole framework with the aid of Mn-catalysis. Independently, Glorius and Ackermann have reacted heteroarenes and arenes with different coupling partners, including vinyl-1,3-dioxolan-2-ones, 2-vinylxiranes, vinylcyclopropanes and diazabicycles. Reaction of indoles with vinyl-1,3-dioxolan-2-ones or 2-vinylxiranes gave the corresponding 2-substituted indoles with incorporation of a C=C bond and an alcohol moiety (Fig. 30). The solvent has been proposed to have a strong influence on this transformation. Glorius found that the reaction can be performed under neat conditions, however the E/Z selectivity for the C=C was improved using Et₂O as solvent (Fig. 30a). H-bonding solvents, 2,2,2-trifluoroethanol and water were chosen (Fig. 30b). Other heterocycles and arenes, substituted with a directing group formed part of a good substrate scope.

![Fig. 30 (a) Mn-catalysed C-H activation reaction of indoles with vinyl-1,3-dioxolan-2-ones reported by Glorius and (b) Ackermann.](image)

A more challenging reaction with vinylcyclopropanes involving a successive C-H/C-C activation process was also reported (Fig. 31). Again slightly different reaction conditions were reported by two groups. Glorius extended the scope to phenylpyridine and thiophene derivatives and Ackermann to pyrroles and amino acid derivatives. Comparable yields were obtained with both methodologies.
In another report by the Glorius group, 2-allenylindoles could be prepared via sequential C-H activation of indoles and internal alkynes (Fig. 32). The regioselectivity of the alkyne insertion was perfectly controlled and further transformation of the obtained 2-allenylindoles, such as cyclisations or polymerisations were avoided. Remarkably 2-allenylindoles containing strong electron withdrawing groups were prepared in excellent yields; other methods to prepare these compounds are rare. Unfortunately, this protocol could not be applied widely to other heterocycles, but could be scaled up to gram quantities with high efficiency.

Three groups have reported methods for the fluoroalkenylation and fluoroallylation of arenes and heteroarenes. Ackermann introduced a strategy for the (per)fluoro alkenylation and allylation that is highly chemo-, regio- and diastereoselective (Fig. 34). [MnBr(CO)₅] allowed the allylative C-F/C-H functionalisation of indoles and arenes with ample scope and wide functional group tolerance (Fig. 34a). It was possible to extend the reaction to the functionalisation of amino acids and structurally complex peptides. 1,1-Difluoroalkenes could also be activated giving the monofluoroalkenylated indoles with high regio- and chemo-selectivity (Fig. 34b). Moreover, the first C-F/C-H functionalisation of ketimines was achieved, again maintaining excellent functional group tolerance and diastereoselectivity (Fig. 34c). Even perfluoroalkenes could be applied in the alkenylation of indoles delivering the E-isomers selectively (Fig. 34d).

The reaction was suggested to occur via a base-assisted cyclomanganation of the indole to form complex I (Fig. 33). The coordination of the carbonyl oxygen of the carbonate leads to intermediate II, which after alkyne insertion gives the 7-membered manganacycle III. The precoordination of the carbonyl oxygen of the carbonate to Mn plays a crucial role in the selectivity of the reaction. This fact was demonstrated by the reaction of indole and a phenylpropyne under standard conditions, which gave the corresponding product, but with alternative regioselectivity. Finally, III suffers a β-oxygen elimination process regenerating the Mn active complex and giving the desired 2-allenylindole.
Fig. 34 Mn-catalysed C-F/C-H (a) allylative functionalisation of indoles; (b) alkenylation with difluoroalkenes; (c) alkenylation of ketimines; and (d) alkenylation with perfluoroalkenes.

The second method was reported by Zhang.\textsuperscript{57} It describes the 3,3-difluoroallylation of indoles and pyridones (Fig. 35). The use of 3-bromo-3,3-difluoropropene as the fluoroallylation source avoided the E/Z selectivity problem. An alternative method was reported by Loh.\textsuperscript{58} Indoles were reacted with gem-difluoroalkenes to afford the corresponding fluoroalkylated indoles (Fig. 36). Other heteroarenes and even arenes were successfully applied, but the yields were lower. E-mono-fluoroalkenes were obtained as the major isomers in most of the cases. Only those substrates with electron-donating substituents or sterically congested ones showed preference for the Z-configuration.

Previous examples with Rh and Co gave only the Z-product in all cases.\textsuperscript{59} The solvent appears to play a crucial role in this unexpected change of selectivity, although the unique reactivity of Mn may also play a part.

3-(Indol-2-yl)succinimide derivatives have also been prepared by Mn-catalysed C-H activation.\textsuperscript{60} Song and co-workers reported the addition of maleimides to indoles (Fig. 37). Addition to pyrroles and arenes was achieved under the same conditions but with modest yield. Maleate ester, ethyl acrylate and 1,4-dihydro-1,4-epoxynaphthalene were compatible coupling partners for this reaction.
The proposed mechanism commences with precoordination of Mn₂(CO)₁₀ to the pyridine moiety on the indole, followed by base-assisted C-H metalation to form complex I (Fig. 38). It is believed that maleimide could act as base in the current catalytic system. Coordination of maleimide to I yields II along with the release of one binding CO. Subsequent insertion of the C=C bond into the Mn-Caryl bond gives the 7-membered intermediate III. Finally, in the presence of another unit of indole, proto-demetalation of III releases the desired product.

The hydroarylation of indoles has been described by Rueping and co-workers very recently.⁶¹ Indoles were reacted with disubstituted allenes in the presence of MnBr(CO)₅ to give 2-substituted indoles (Fig. 39). Excellent yields were obtained and a good functional group tolerance was evident.

The mechanism described by Rueping begins with the reaction of NaOAc and MnBr(CO)₅ to generate the active [Mn] species (Fig. 40). C-H activation affords the well-known complex I, which is followed by allene insertion into the manganese-carbon bond. Subsequent protonation gives the hydroarylation product.

Unexpected reactivity was observed when tri-substituted allenes were employed (Fig. 41a).⁶¹ This interesting cascade reaction was also reported by Wang and co-workers (Fig. 41b).⁶²
The C-H alkenylation process is followed by a Smiles rearrangement affording the corresponding pyrroloindolone product. The mechanistic scenario proposed by Wang for this transformation is initiated, as usual, by pyridinyl-assisted, Mn-catalysed C-H activation (Fig. 42).

Intermediate II then coordinates to the allene which undergoes a regio- and stereoselective migratory insertion, generating IV. Protonation of IV may result in the formation of the alkenylation product. Alternatively, the strong nucleophilicity of C-Mn could lead to 1,4-migration of the directing group. Finally, an intramolecular displacement of the ethoxyl group from the ester, furnishes the pyrroloindolone. Wang extended his protocol to di-substituted allenes in order to prepare alkylated arenes and heteroarenes (Fig. 43).63

Bromoallenes have been used for the propargylation of heteroarenes using a co-catalytic system with a combination of Mn, and BPh₃ as a Lewis acid (Fig. 44).64 Terminal and internal alkenes can be obtained by this methodology.

Recently Ackermann has accomplished the first combination of synergistic Brønsted acid/Mn-catalysis and flow chemistry for the hydroarylation of indoles (Fig. 45).65 This methodology allows the preparation of the corresponding products in less than 20 minutes. The reaction could be performed in batch also adapting the reaction conditions. Moreover, the use of the synergistic Brønsted acid/Mn-catalysis enabled the chemoselective hydrogenations using alkenes with β-O leaving groups, preventing the β-O-elimination process.
Finally, Glorius has reported very recently an unprecedented Mn-catalysed (2-indolyl)methylation of heteroarenes. This methodology allows the synthesis of challenging unsymmetrical diheteroarylmethanes through an aromatization cascade reaction.

Fig. 45 Synergistic Brønsted acid/Mn-catalysed in continuous flow.

Conclusions and Outlook

Mn-catalysed C-H activation is a quickly emerging area of organic synthesis. A number of powerful transformations are now possible involving the functionalization of rather inert C-H bonds using Mn-based catalysts. So far, sustainability and cost of manganese metal provides great hope that Mn-derived catalysts may challenge platinum-group-metal catalysts in the future. Additionally, reactivity has been observed using catalysts such as MnBr(CO)$_5$, not present using many of the commonly-utilised, powerful, Ru/Rh based catalysts. Finally, the catalytic cycles published to date largely operate in an isohypsic fashion and thus require no added oxidant.

All that said, a number of hurdles remain. The limitations of Mn-catalysis include the reliance on directing groups in most cases, and the substrate scope is sometimes limited. Additionally, conditions remain rather harsh and elevated temperatures are usually required. Green solvents have not been widely applied. Additionally, almost all the reports to date rely on [$\text{MnBr(CO)}_5$] and [$\text{Mn}_2(\text{CO})_{10}$] complexes as the pre-catalytic species. Thus little is known about the effect of other ligands on Mn. Given that ligand development has had a critical effect on the progression of Pd (and other) catalysed coupling, this area will surely be the main route to expansion and exploitation of Mn-catalysis. Further, mechanical insight is certainly required. For example, while good evidence for 5- and 7-membered manganacycles, as key reaction intermediates, has been provided relatively little is known about the entire catalytic cycle and further investigation is needed. Many reports indicate that C-H bond breakage is not rate determining, and thus a focus on insertion and elimination steps might be rewarding. Asymmetric transformations which utilise Mn-catalysts are in their infancy and again ligand development will play a role here. Finally, the design of a recyclable heterogeneous Mn catalysts would further enhance the practical utility of manganese-based catalytic systems.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

5. Palladium price in June 2017 was 27.84 $/kg.
8. For manganese prices see: http://www.infomine.com/investment/metal-prices/manganese/. Manganese price in June 2017 was 1.97 $/kg.


