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

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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.[1] Within the pharmaceutical industry, palladium, without doubt, plays the most prominent role among the precious metals.[2] However, Pd is rare in the Earth´s crust (0.89 ppm)[3] and its cost is steadily increasing.[4] 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).[5] 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[3] and the third most abundant transition metal after iron and titanium. The low toxicity[6] and low cost[7] 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.[8] For instance, several manganese containing enzymes are essential for metabolizing carbohydrates, cholesterol, and amino acids in the human body.[5, 9] Overall it demonstrates a far lower health and environmental impact than platinum group metals.[10]

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C-H activation represents a challenging, yet highly rewarding methodology, in modern synthetic chemistry (Fig. 1).[11] 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).[12] 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).[13]

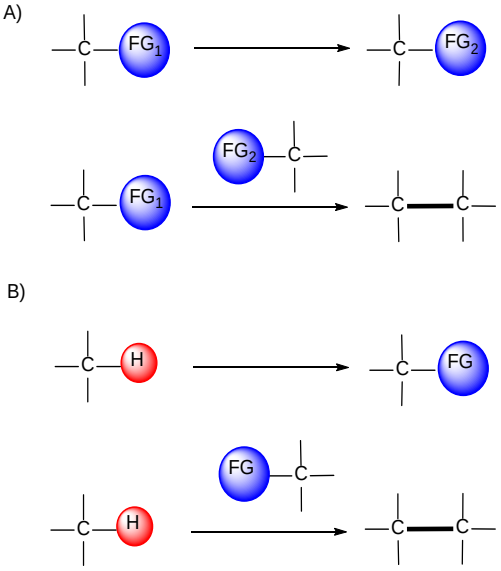


Fig. 1 (A) Traditional functional group transformation and (B) C-H bond activation methodology.

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[14] natural product synthesis[15] and material sciences.[16] 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.[17] In particular, the advantages of modern C-H activation methods to synthesise aromatic and heteroaromatic compounds via C-H activation[18] are among the published 'Wanted List' of top pharmaceutical companies.[19] Undoubtedly the C-H activation field has been dominated by catalysts based on noble transition metals such as ruthenium, rhodium, palladium, iridium or platinum.[20] Using these 4d and 5d transition metals, some strides have been made towards more sustainable C-H activation modes, for example, using mild conditions[21] or heterogeneous catalysts.[22] 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.[23] Among these, manganese[24] 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.[25] 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 d^6 configurations and typically feature very strong crystal field ligands such as carbonyl.[26] 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 PR_3. 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: $Mn(CO)_5Br$ and $Mn_2(CO)_{10}$.

On the other hand, manganese catalysed C-H oxygenations,[27] nitrogenations[28] and halogenations[29] 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,[30] and stoichiometric transformations by Liebeskind,[31] Nicholson and Main,[32] and Woodgate,[33] key contributions involving catalysis, from the groups of Kuninobu/Takai,[34] Wang,[35] Ackermann,[36] and others[37] have changed the landscape of Mn-catalysis. Various manganese catalysed C-H allylations, C-H alkenylations, 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, alkenes, 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.[24b]

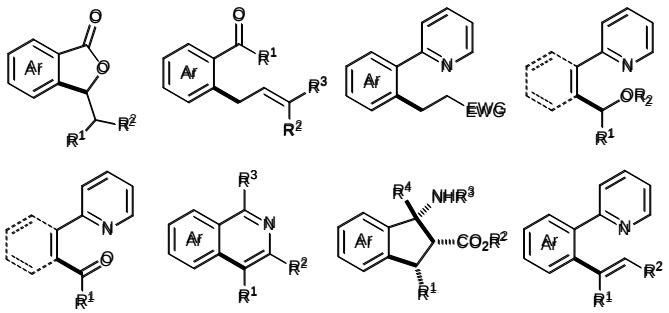


Fig. 2 C-C bonds formed by Mn-catalysed C-H activations.

Since the publication of an excellent review on Mn mediated C-H activation by Ackermann in 2016,[24b] 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.[38] 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 $[Mn_2(CO)_{10}]$ and $[MnBr(CO)_5]$ 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.

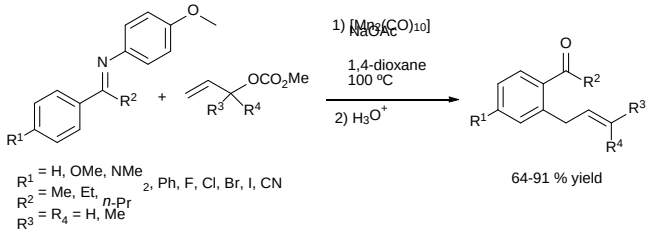


Fig. 3 Mn-catalysed C-H allylation of imines.

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.

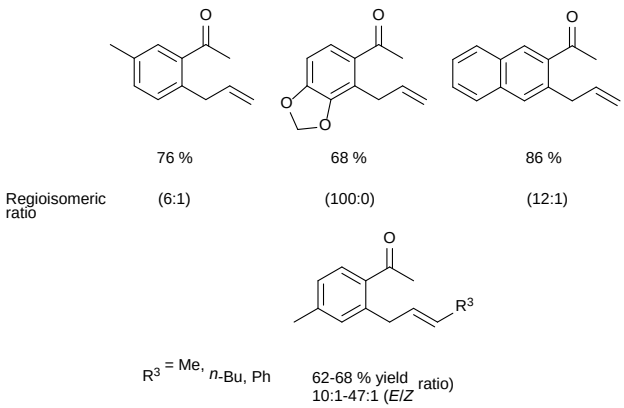


Fig. 4 Regio- and stereocontrol of the C-H allylation of imines (only major regioisomer shown).

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 intermolecular 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.

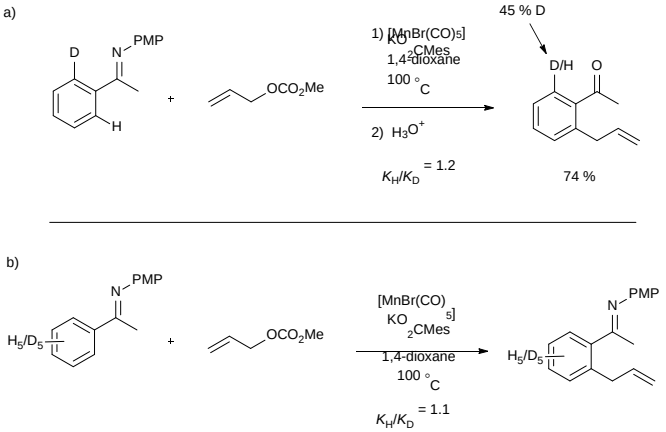


Fig. 5 (a) Intra- and (b) intermolecular KIE experiments.

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.

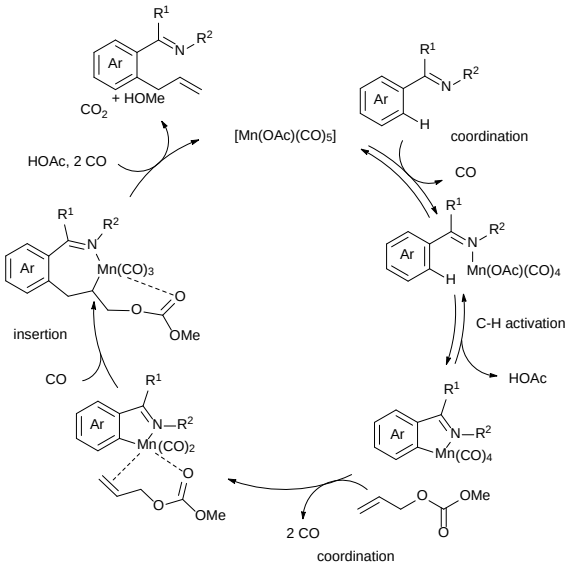
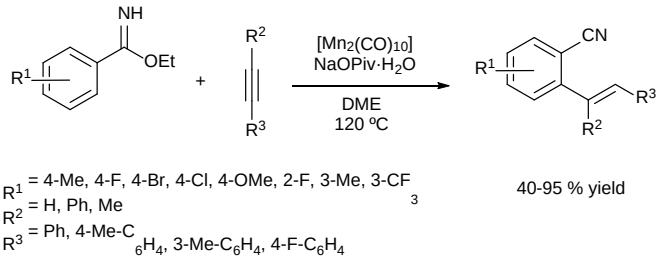


Fig. 6 Proposed mechanism for the Mn-catalysed C-H allylation of arenes.

A β-hydride elimination then gives the corresponding product, while decarboxylation and salt metathesis regenerates the Mn-complex. Although the dimeric complex $[Mn_2(CO)_{10}]$ 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 alkyne, the cyano group is unmasked to reveal the corresponding *o*-alkenylated 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.



R^1 = 4-Me, 4-F, 4-Br, 4-Cl, 4-OMe, 2-F, 3-Me, 3-CF_3
R^2 = H, Ph, Me
R^3 = Ph, 4-Me-C_6H_4, 3-Me-C_6H_4, 4-F-C_6H_4

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 alkyne-insertion of the Mn-C bond affording the seven-membered manganacycle **III** via the alkyne–Mn complex **II**. Two pathways are then proposed depending on whether the alkyne is terminal or internal. For terminal alkynes (path A), a second alkyne 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 and **VI**, which undergoes an alkynyl-assisted C-H activation to regenerate intermediate **II**. For internal alkynes, the direct protonation of the Mn-$C_{alkenyl}$ bond of **III** affords the alkenylated benzimidate. Subsequent complexation of substrates and C-H activation of the benzimidate in the presence of NaOPiv regenerates **II**.

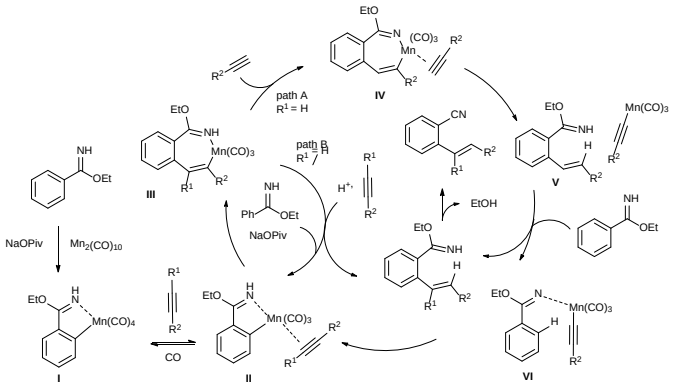
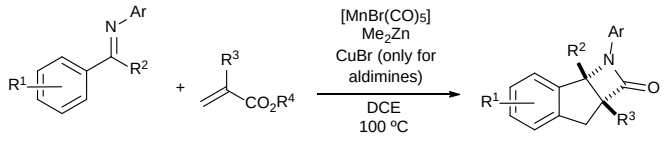


Fig. 8 Proposed mechanism for the Mn-catalysed C-H alkenylation of imidates.

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.



R^1 = H, 4-Me, 4-F, 4-Br, 4-Cl, 4-OMe, 4-CF_3, 3-Me, 2-Me
R^2 = H, Ph, Me, Et
R^3 = H, Me
R^4 = Me, Et, *n*-Bu, *t*-Bu, 2-Et-hexyl
Ar = Ph, 4-MeO-C_6H_4, 4-F-C_6H_4

Fig. 9 Mn- and Zn-catalysed bicyclic annulation of imines with α,β-unsaturated esters.

Based on several experiments performed, a bimetallic catalytic cycle was proposed by the authors (Fig. 10). Firstly $[MnBr(CO)_5]$ reacts with Me_2Zn 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 Me_2Zn 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.

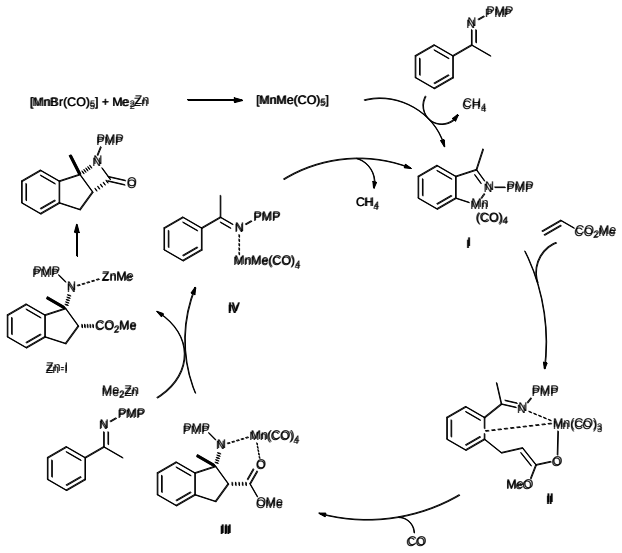
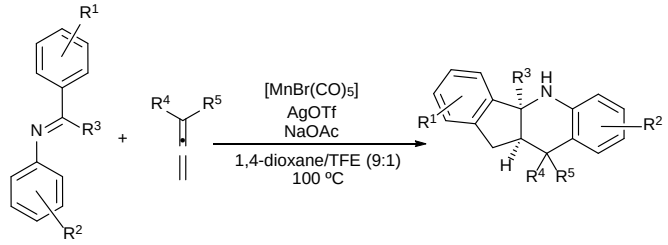


Fig. 10 Proposed mechanism for the Mn- and Zn-catalysed bicyclic annulation of imines with α,β-unsaturated esters.

A further example of bimetallic catalysis was reported by Wang and co-workers.[41] 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.



R^1 = H, 4-Me, 4-F, 4-Br, 4-CN, 2-Cl, 3-Cl
R^2 = H, 4-OMe, 4-Me, 4-F, 4-I, 3-OMe, 2-Me
R^3 = H, Me, Et
R^4 = Me, Ph, Bn, *n*-hexyl
R^5 = Me
R^4R^5 = -$(CH_2)_5$

Fig. 11 One pot Mn-catalysed C-H allylation and Ag-catalysed Povarov cyclisation.

The process is initiated by C-H activation, assisted by the imine as directing group to form intermediate **II** (Fig. 12). This step is believed to be reversible and not turn-over limiting, and presumably taking place through a σ-complex-assisted metathesis or base-assisted electrophilic substitution. Thereafter, allene coordination and subsequent *Z*-selective migratory insertion of the terminal double bond of the allene from the less-shielded π-face provides **IV**. Protonation of the C-Mn bond releases the Mn catalyst and gives the allylation product **V**. Then Ag-catalysed Povarov cyclisation delivers intermediate **VI** via **TS-I** and after aromatisation, the final product is obtained.

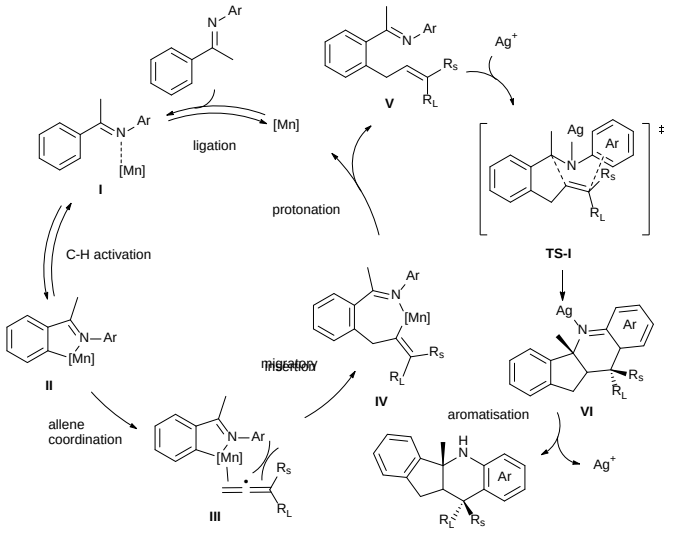


Fig. 12 Proposed mechanism for the Mn-catalysed C-H allylation and Ag-cataysed Povarov cyclisation.

A related methodology was described by Ackermann and co-workers.[42] Similar products could be prepared using methylenecylcopropanes instead of allenes, by using a combination of Mn- and Zn-catalysis (Fig. 13).

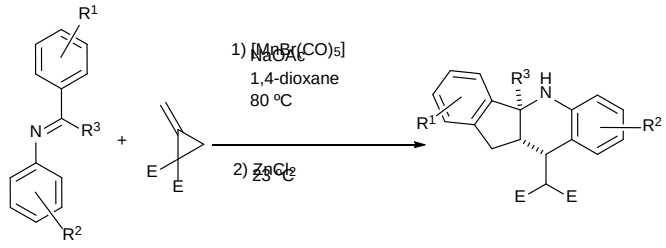


Fig. 13 Mn-catalysed C-H activation with methylenecyclopropane and Zn-catalysed Povarov cyclisation.

Manolikakes' group reported a $Mn(OAc)_3$-promoted cross-dehydrogenative coupling of sodium and lithium sulfinates with 1,4-dimethoxybenzenes (Fig. 14).[43] 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.

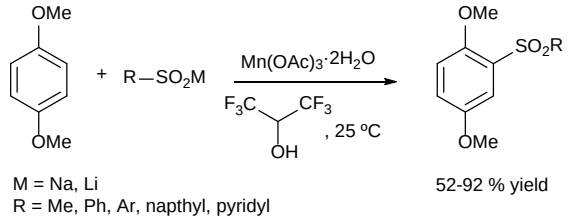


Fig. 14 C-H sulfonylation of 1,4-dimethoxybenzenes.

Alkylations with β-hydrogen-containing alkyl halides were also accomplished via Mn-catalysed C-H activation (Fig. 15).[44] In this work $MnCl_2$ 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 group (TAM) was mandatory. The use of tertiary amides was unsuccessful.

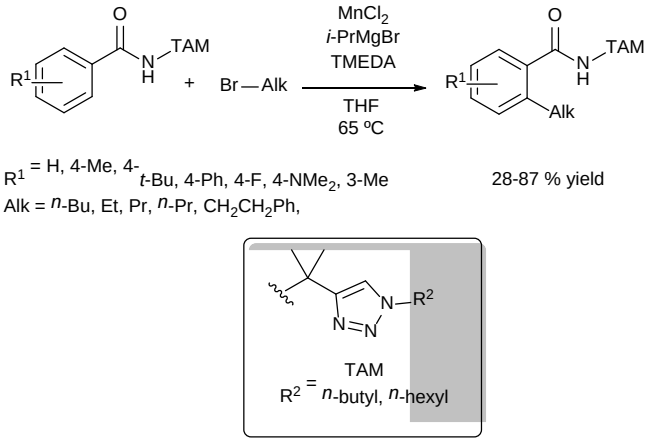


Fig. 15 Mn-catalysed C-H alkylation of benzamides.

A new strategy to prepare isoquinolines and isoquinolones has been reported by the Glorius group.[45] 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).

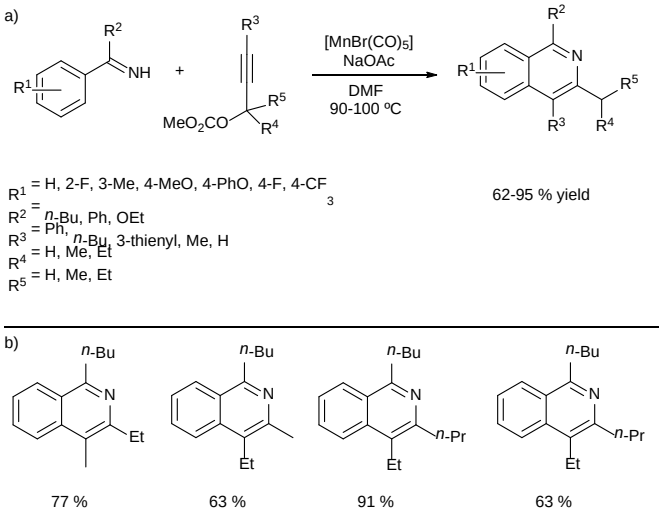


Fig. 16 (a) Mn-catalysed regioselective synthesis of isoquinolines; (b) control of regioselectivity in isoquinolines.

The reaction probably commences with base assisted cyclomanganation of the imine forming a 5-membered manganacycle **I** (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**.

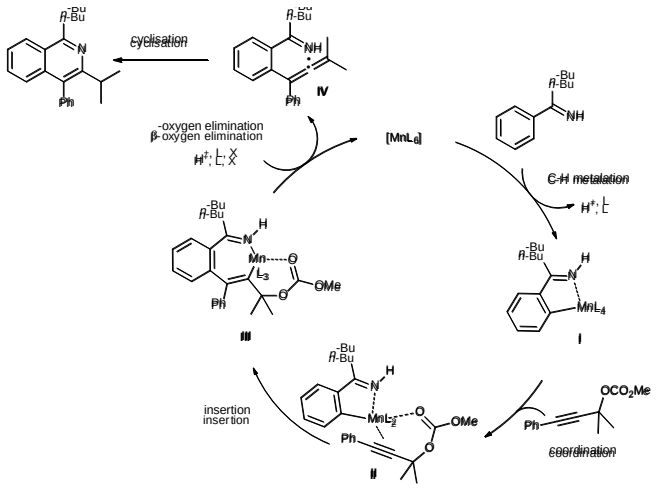


Fig. 17 Proposed mechanism for the Mn-catalysed synthesis of isoquinolines.

The Mn-catalysed directed methylation of alkenes has been reported by Nakamura's lab using $MnCl_2 \cdot 2LiCl$ and MeMgBr.[46] 1-Bromo-2-chloroethane was also needed as a mild oxidant. This system is applicable to aromatic, heteroaromatic and olefinic secondary amide substrates (Fig. 18). When two different *ortho*-positions are available, it is possible to achieve the mono- or the di-methylated products depending on the amount of MeMgBr and 1-bromo-2-chloroethane used.

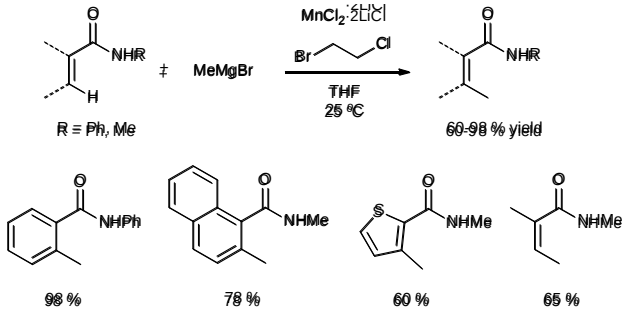


Fig. 18 Mn-catalysed directed methylation of C(sp^2)-H bonds.

A very interesting reaction has been described by Wang and co-workers.[47] 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).

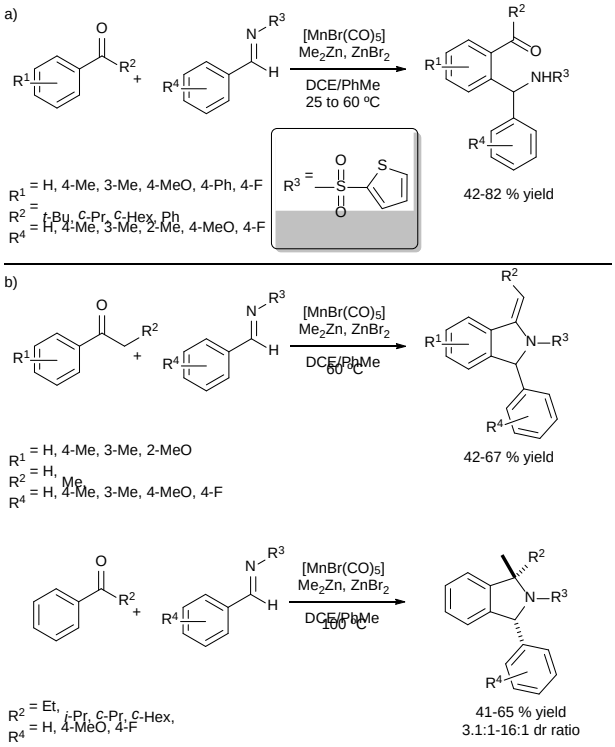


Fig. 19 (a) Mn-catalysed addition of ketones to imines; (b) Mn-catalysed C-H activation for the selective preparation of exo-olefinic isoindoline and three-component methylated isoindolines.

The mechanism proposed by the authors starts with the formation of $[MnMe(CO)_5]$ from $[MnBr(CO)_5]$ and Me_2Zn (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 Me_2Zn 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 Me_2Zn forms the isoindoline.

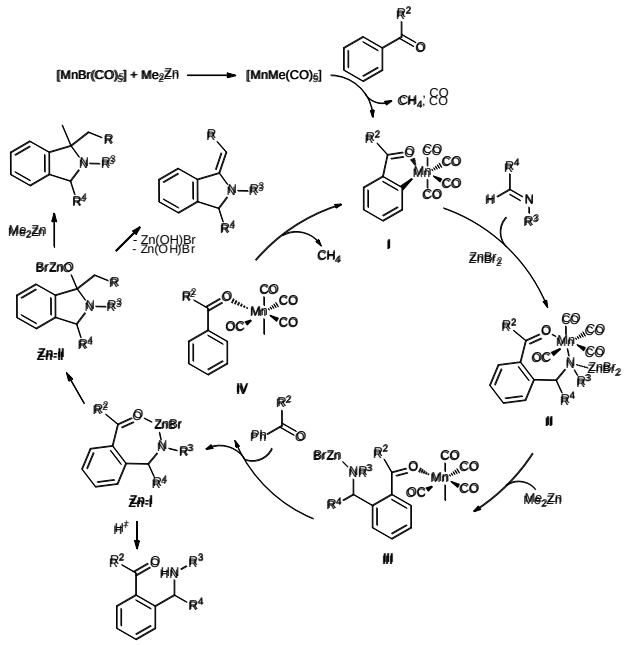
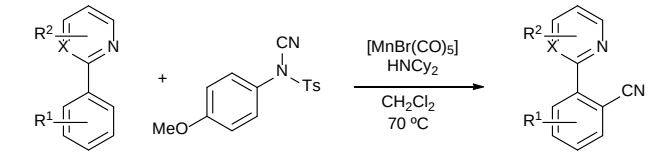


Fig. 20 Mechanism for the Mn-catalysed addition of ketones to imines.

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).[48]



R^1 = H, 4-OMe, 2-OMe, 4-F, 4-Cl, 4-CF_3, 3-Me
R^2 = 3-Me, 4-Me, 5-Me, 5-CF_3
X = CH, N

27-79 % yield

Fig. 21 Manganese-catalysed C-H cyanation of arenes.

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≡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.

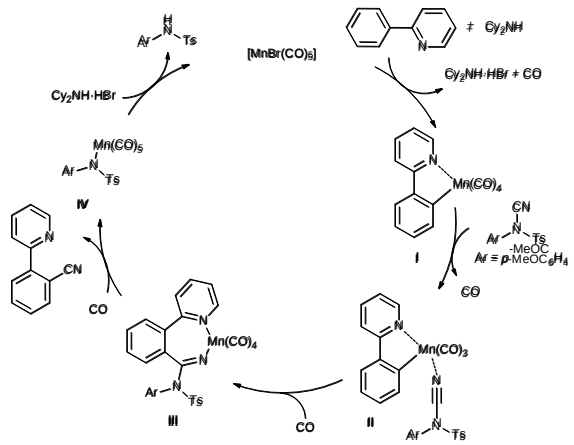


Fig. 22 Proposed mechanism for the cyanation of arenes

C-H Activation of Heteroarenes

Recently, a very interesting study has been reported by Fairlamb and co-workers.[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.

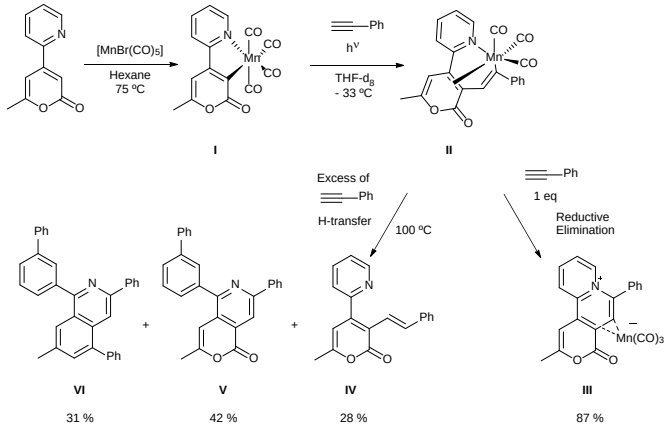


Fig. 23 Study of Mn-catalysed C-H activation of 2-pyrones.

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.

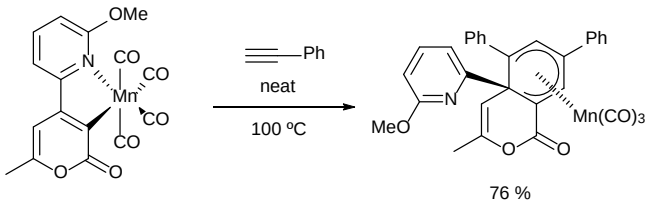


Fig. 24 Double alkyne insertion.

Ackermann reported the hydroarylation of carbon-heteroatom multiple bonds using manganese catalysis and without the addition of additives (Fig. 25a).[50] Remarkably $[Mn_2(CO)_{10}]$ and $[MnBr(CO)_5]$ showed an unprecedented selectivity for the C-2 position of indoles. For comparison, other transition metal-based systems tested give 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).

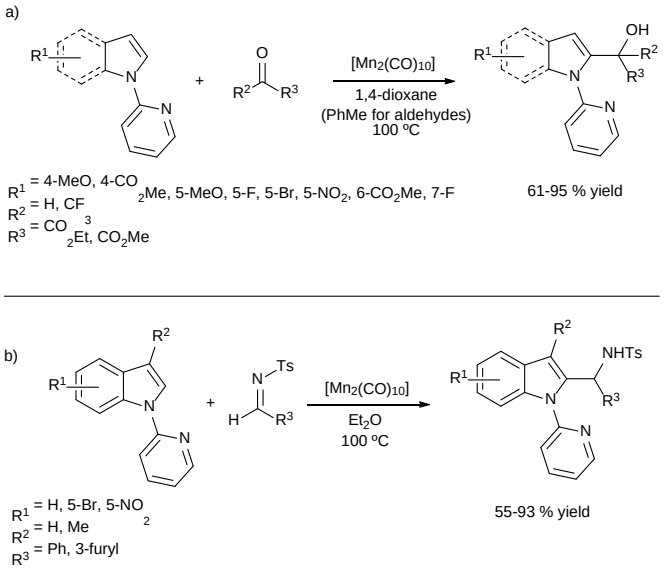


Fig. 25 (a) Mn-catalysed C-H hydroarylation of C=Het; (b) C-H activation with imines.

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 demetalation, the final product was produced and complex **I** is regenerated. C-H metalation occurring by a metal-assisted σ-bond metathesis by a ligand-to-ligand hydrogen transfer was proposed to explain the selectivity.

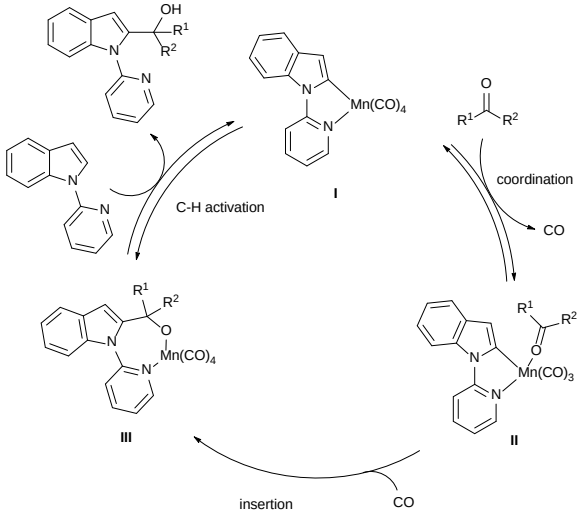


Fig. 26 Proposed mechanism for the Mn-catalysed hydroarylation of heterocycles.

The same group reported the C-H cyanation of heterocycles by means of synergistic heterobimetallic catalysis.[51] 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.

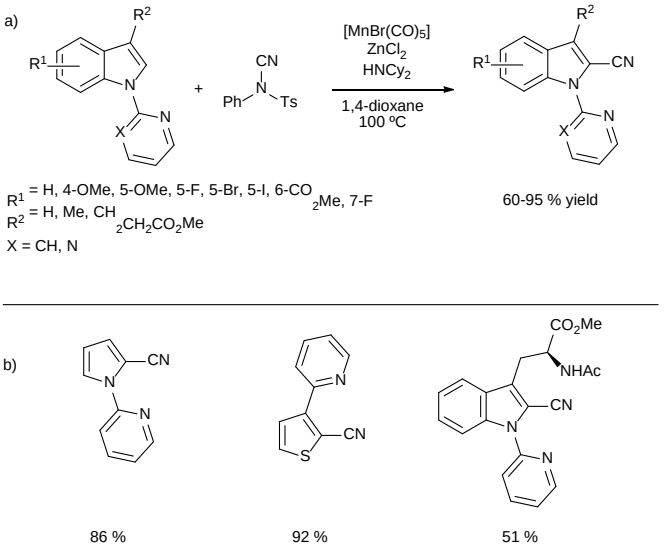


Fig. 27 (a) Mn-catalysed C-H cyanation of simple indoles; (b) C-H cyanation of other heterocycles.

Ackermann and co-workers also reported the C-H alkynylation of indoles and pyrroles in the presence of $[MnBr(CO)_5]$ (Fig. 28).[52] Silyl 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 BPh_3. As usual in Mn-catalysis the protocol was fully tolerant of valuable functionalities, including halogen, ester, cyano and nitro groups. 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.

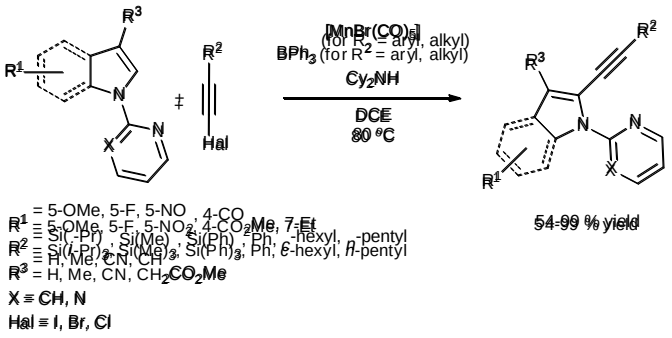


Fig. 28 Mn-catalysed C-H alkynylation.

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.

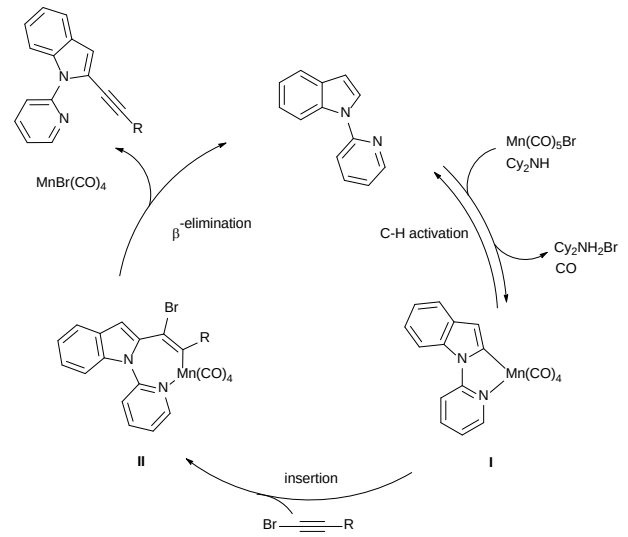


Fig. 29 Proposed mechanism for the Mn-catalysed C-H alkynylation.

Other functionalisations have been incorporated into the indole framework with the aid of Mn-catalysis. Independently, Glorius[53] and Ackermann[54] have reacted heteroarenes and arenes with different coupling partners, including vinyl-1,3-dioxolan-2-ones, 2-vinyloxiranes, vinylcyclopropanes and diazabicycles. Reaction of indoles with vinyl-1,3-dioxolan-2-ones or 2-vinyloxiranes 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 Et_2O 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.

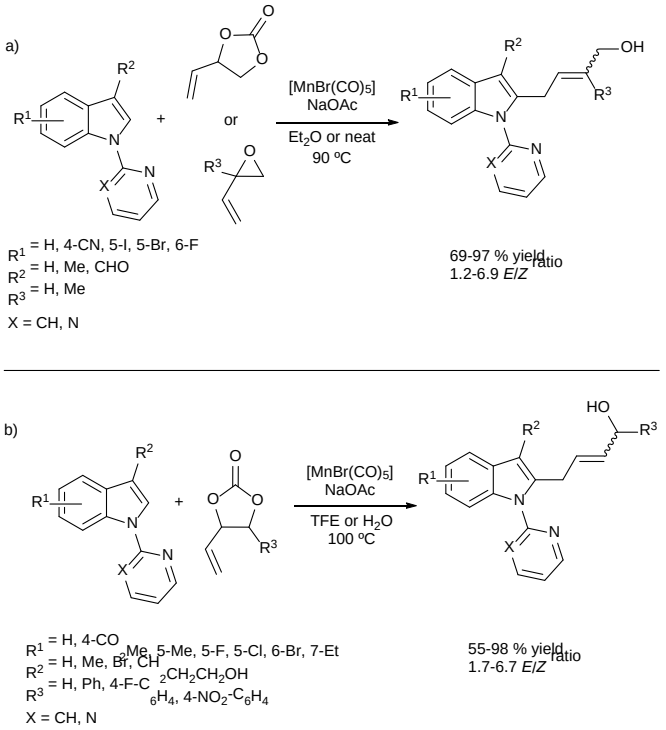


Fig. 30 (a) Mn-catalysed C-H activation reaction of indoles with vinyl-1,3-dioxolan-2-ones reported by Glorius[53] and (b) Ackermann.[54b]

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[53] and Ackermann to pyrroles and amino acid derivatives.[54a] Comparable yields were obtained with both methodologies.

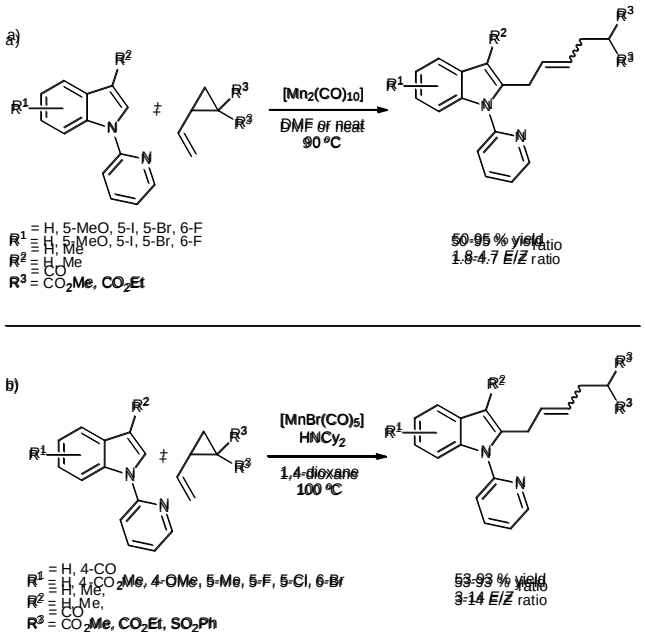


Fig. 31 (a) Mn-catalysed C-H/C-C activation reaction of indoles with vinylcyclopropanes reported by Glorius[53] and (b) reported by Ackermann.[54a]

In another report by the Glorius group, 2-allenylindoles could be prepared via sequential C-H activation of indoles and internal alkynes (Fig. 32).[55] 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.

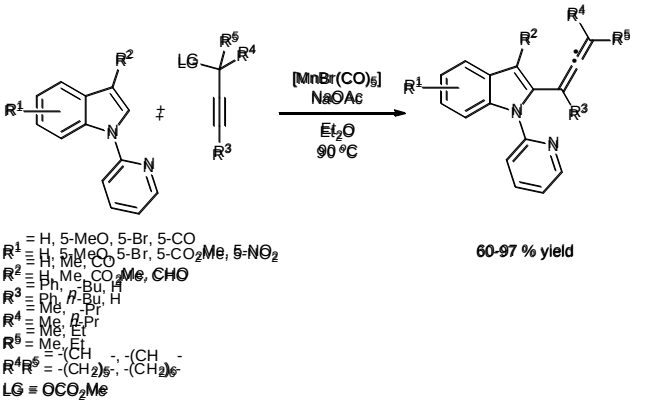


Fig. 32 Mn-catalysed C-H allenylation.

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.

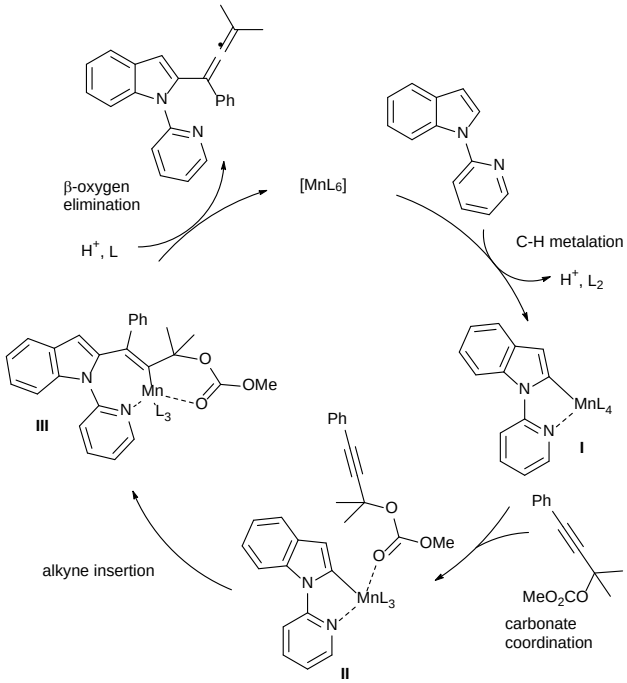


Fig. 33 Proposed mechanism for the Mn-catalysed C-H allenylation.

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).[56] $[MnBr(CO)_5]$ 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).

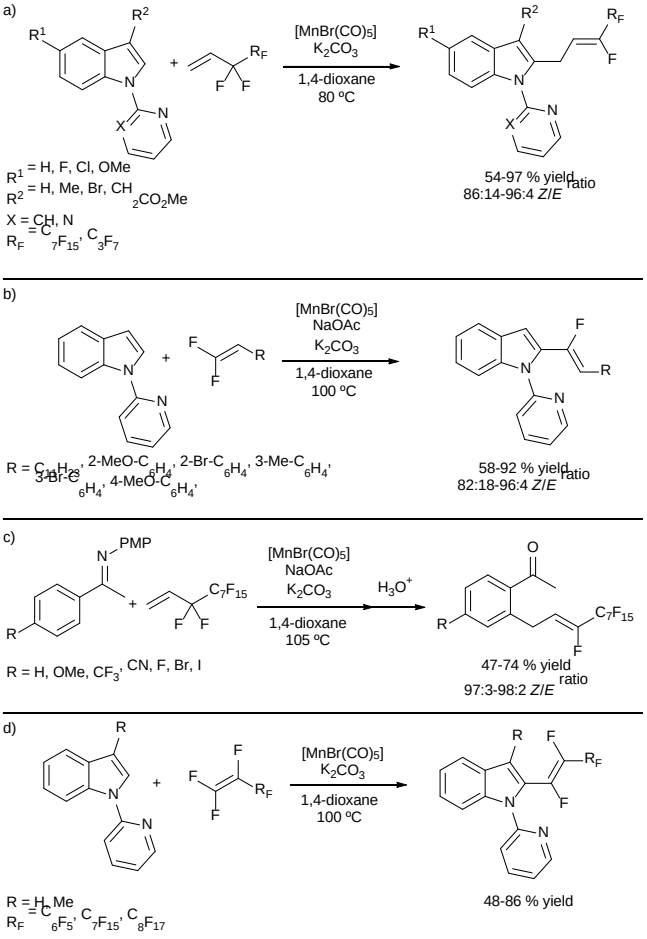


Fig. 34 Mn-catalysed C-F/C-H (a) allylative functionalisation of indoles; (b) alkenylation with difluoroalkenes; (c) allylative functionalisation of ketimines and (d) alkenylation with perfluoroalkenes.

The second method was reported by Zhang.[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.[58] Indoles were reacted with *gem*-difluoroalkenes to afford the corresponding fluoroalkenylated indoles (Fig. 36). Other heteroarenes and even arenes were successfully applied, but the yields were lower. The presence of the fluorine atoms was required for the reaction to proceed. Surprisingly the thermodynamically less stable *E*-monofluoroalkenes 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.

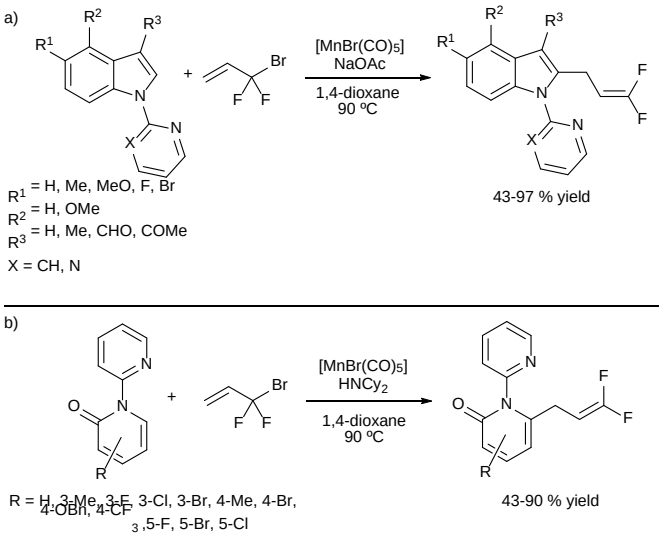


Fig. 35 Mn-catalysed C-H 3,3-difluoroallylation of (a) indoles and (b) pyridones.

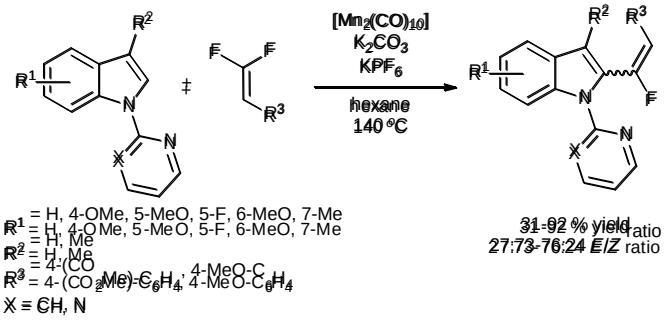


Fig. 36 Mn-catalysed α-fluoroalkenylation of indoles via C-H activation.

Previous examples with Rh and Co gave only the *Z*-product in all cases.[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.[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.

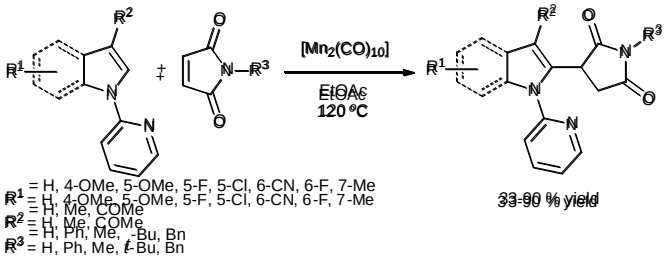


Fig. 37 Mn-catalysed addition of indoles and pyrroles to maleimides.

The proposed mechanism commences with precoordination of $Mn_2(CO)_{10}$ 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-C_{aryl} bond gives the 7-membered intermediate **III**. Finally, in the presence of another unit of indole, proto-demetalation of **III** releases the desired product.

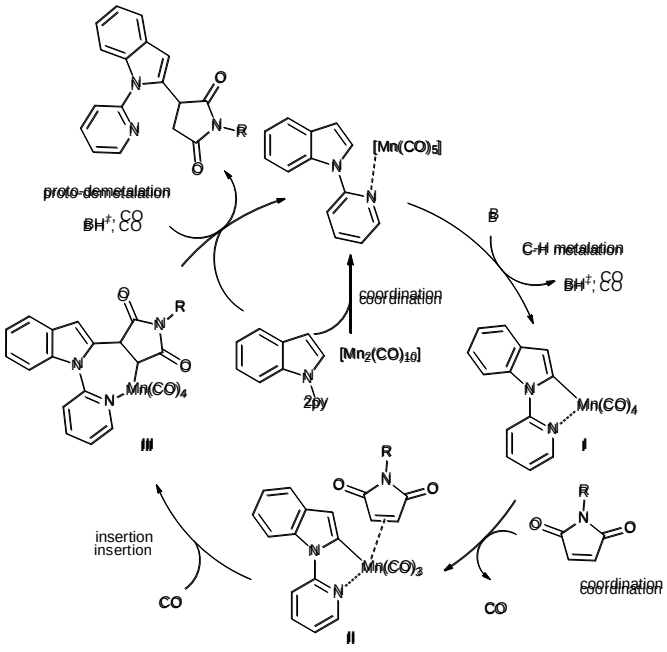


Fig. 38 Proposed mechanism for the Mn-catalysed addition of maleimides to indoles.

The hydroarylation of indoles has been described by Rueping and co-workers very recently.[61] Indoles were reacted with di-substituted 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.

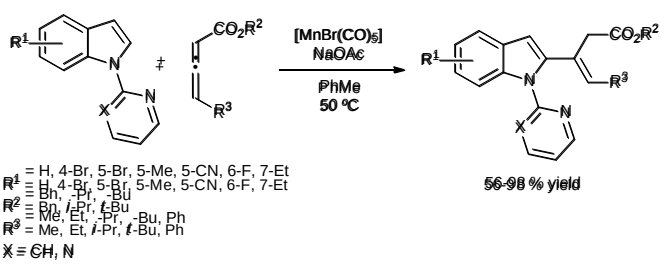


Fig. 39 Mn-catalysed C-H hydroarylation of indoles with di-substituted allenes.

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.

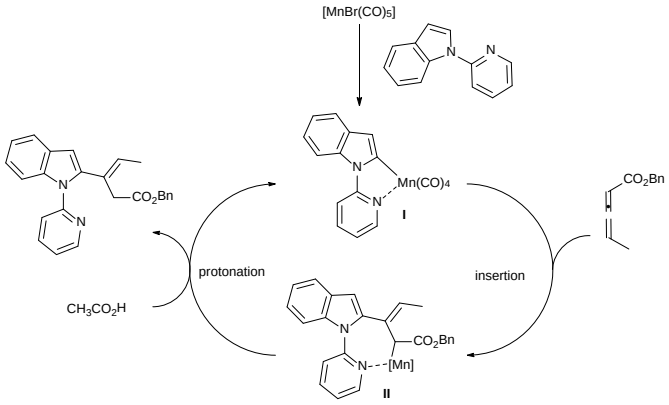


Fig. 40 Proposed mechanism for the Mn-catalysed hydroarylation of indoles.

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]

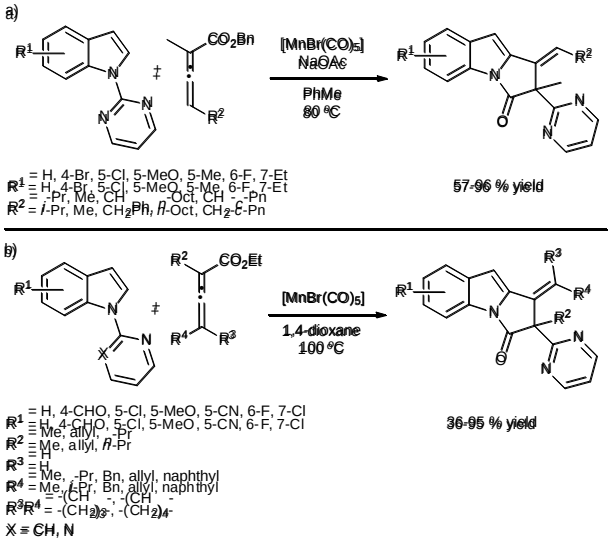


Fig. 41 Mn-catalysed C-H alkenylation/Smiles rearrangement cascade reaction reported by (a) Rueping[61] and (b) Wang.[62]

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).

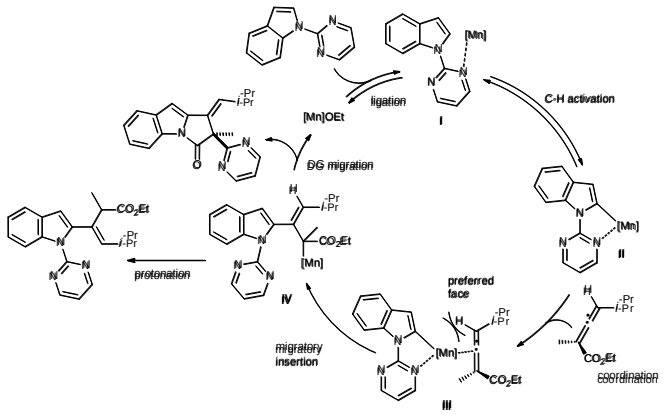


Fig. 42 Proposed mechanism for the Mn-catalysed C-H alkenylation/Smiles rearrangement cascade reaction.

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 allylated arenes and heteroarenes (Fig. 43). [63]

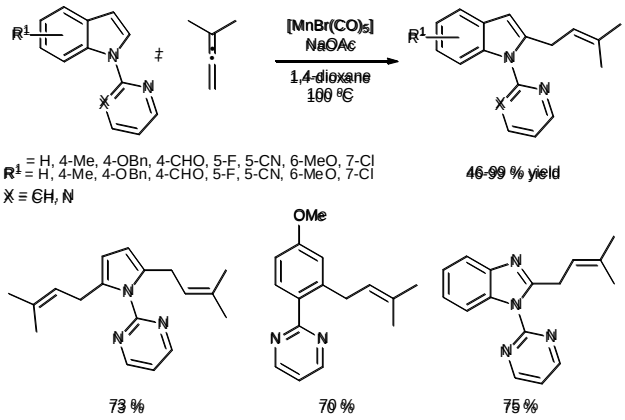


Fig. 43 Mn-catalysed C-H allylation of arenes with allenes.

Bromoallenes have been used for the propargylation of heteroarenes using a co-catalytic system with a combination of Mn, and BPh_3 as a Lewis acid (Fig 44).[64] Terminal and internal alkynes can be obtained by this methodology.

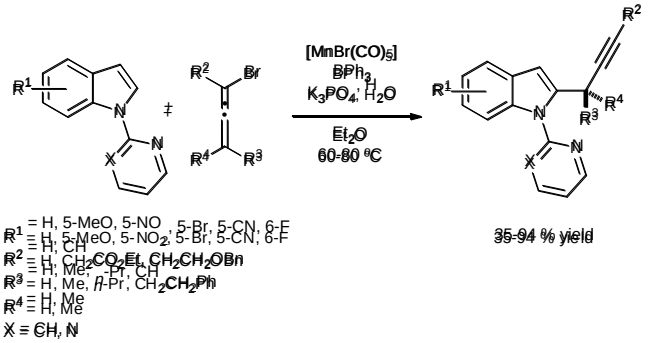


Fig 44 Mn- and Lewis acid-catalysed propargylation of heteroarenes.

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 hydroarylations using alkynes with β-O leaving groups, preventing the β-O-elimination process.

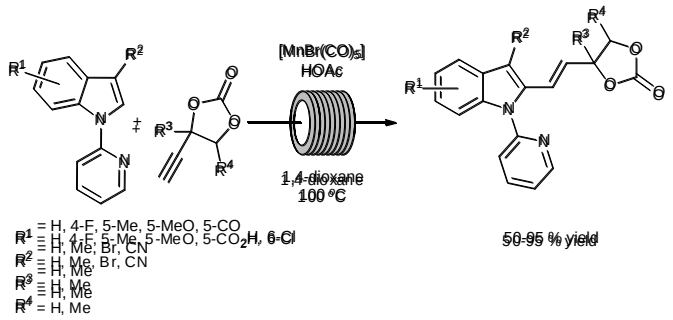


Fig. 45 Synergistic Brønsted acid/Mn-catalysed in continuous flow.

Finally, Glorius has reported very recently an unprecedented Mn-catalysed (2-indolyl)methylation of heteroarenes.[66] This methodology allows the synthesis of challenging unsymmetrical diheteroarylmethanes through an aromatization cascade reaction.

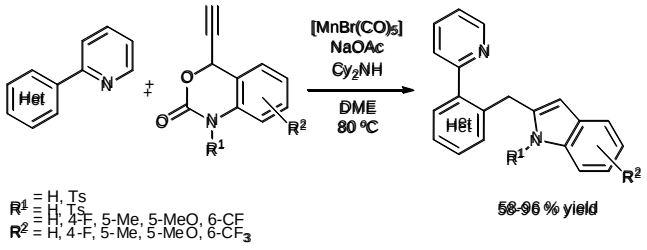


Fig. 46 Mn-catalysed (2-indolyl)methylation.

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 $[MnBr(CO)_5]$ and $[Mn_2(CO)_{10}]$ 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. Finally, further mechanistic 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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