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A manganese(I)tricarbonyl-catalyst for near room temperature alkene and alkyne hydroarylation†

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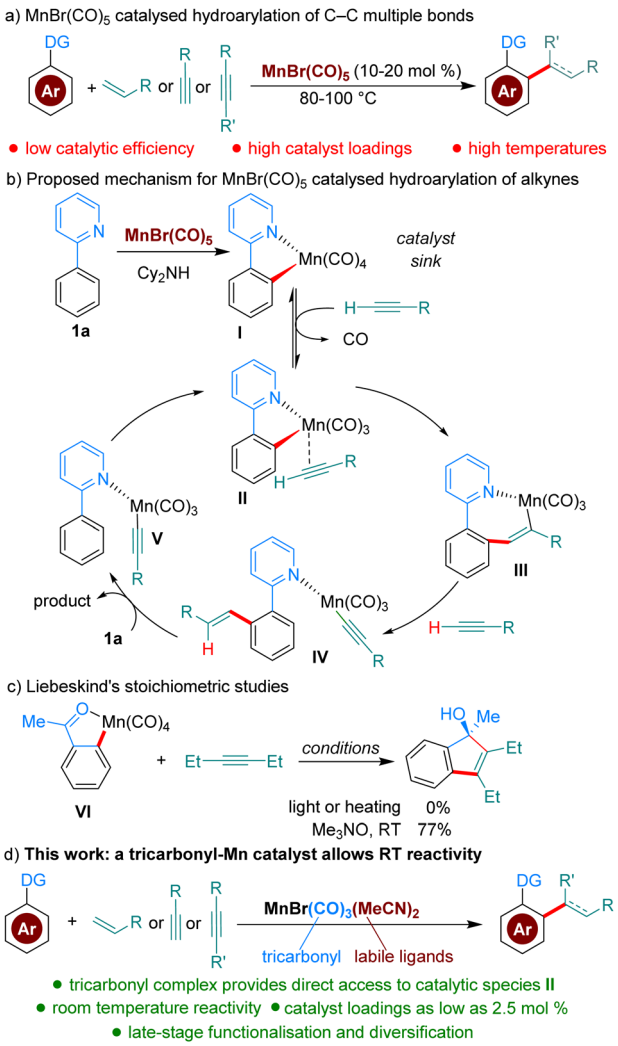
Developing more efficient catalytic processes using abundant and low toxicity transition metals is key to enable their mainstream use in synthetic chemistry. We have rationally designed a new Mn(I)-catalyst for hydroarylation reactions that displays much improved catalytic activity over the commonly used $MnBr(CO)_5$. Our catalyst, $MnBr(CO)_3(MeCN)_2$, avoids the formation of the off-cycle manganacycle-$(CO)_4$ species responsible for low catalyst activity, allowing near room temperature hydroarylation of alkenes and alkynes with broad functional group tolerance including late stage functionalisation and diversification of bioactive molecules.

Introduction

C–H functionalisation bears the promise of streamlining synthetic organic procedures, resulting in more sustainable processes.[1] The field of C–H functionalisation has traditionally been dominated by precious metals; however, in recent years many base-metal catalysed processes have been developed.[2] Mn in particular, the third most abundant transition metal and of low toxicity, has received much attention as a catalyst.[2a,3] Mn-catalysed hydroarylation reactions of C–C multiple bonds are among the most studied methods (Scheme 1a). However, these reactions, which are almost invariably catalysed by either $MnBr(CO)_5$ or $Mn_2(CO)_{10}$, suffer from low catalytic activity, resulting in the requirement of elevated temperatures (80–100 °C) and high catalyst loadings (commonly 10–20 mol%).[4] Based on computational and experimental studies, Wang and co-workers have proposed a mechanism where $MnBr(CO)_5$ is a precatalyst forming off-cycle species **I** (Scheme 1b), which must dissociate CO and coordinate the alkyne coupling partner to enter the catalytic cycle as **II**. The authors calculated that the formation of **II** from **I** is disfavored by 22.5 kcal mol^{-1}.[5] More recently, Fairlamb, Lynam and co-workers were able to further experimentally characterize, with time-resolved infrared spectroscopy, the dissociation and association processes going from **I** to **III**, by facilitating the dissociation of CO through photochemical activation.[6] Interestingly, Liebeskind showed in 1989 that $Mn(CO)_4$-complex **VI** is unreactive towards alkynes.[7] However, when a stoichiometric amount of a CO scavenger is added, the desired product is formed at room temperature, demonstrating the higher reactivity of $Mn(CO)_3$-species. The



Scheme 1 Mn-catalysed hydroarylations of C–C multiple bonds.

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group of Woodgate further expanded on these studies, using stoichiometric Mn-complexes and CO scavengers in the modification of steroid derivatives.[8]

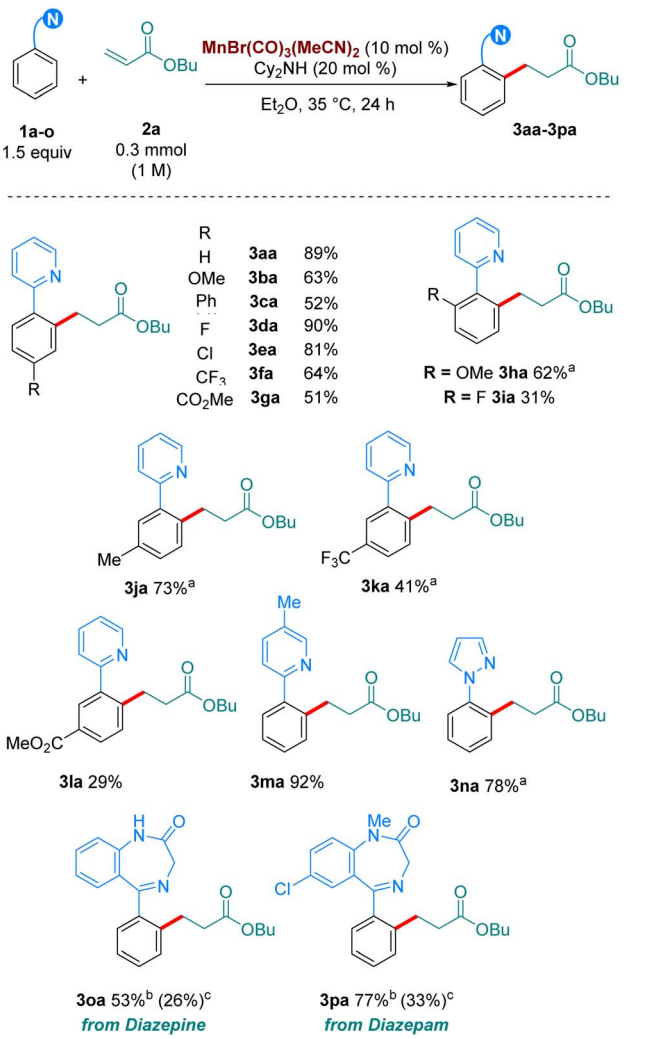
Based on the studies described above, we reasoned that in the reaction conditions for hydroarylation, $Mn(CO)_4$-species **I** are acting as an off-cycle catalyst 'sink' responsible for the low catalyst efficiency. We hypothesised that a stable $MnXL_2(CO)_3$-species with appropriate L ligands, could result in significantly enhanced catalytic activity, by avoiding altogether the formation of off-cycle species **I**. To the best of our knowledge $Mn(CO)_3$-complexes have never been reported as catalysts for hydroarylation reactions. Herein, we describe a novel catalytic hydroarylation that takes advantage of a Mn-complex capable of mediating these reactions at room temperature or near room temperature, overcoming one of the current bottlenecks in efficient Mn-catalysis (Scheme 1d).

Results and discussion

To test our hypothesis, we chose as a benchmark the reaction between 2-phenylpyridine, **1a**, and butyl acrylate, **2a**, previously requiring 100 °C when catalysed by $MnBr(CO)_5$. We began our studies by synthesising several Mn(I)-tricarbonyl complexes to test in our reaction manifold. Gratifyingly, upon testing these complexes at 35 °C, we found that all of them displayed superior reactivity to $MnBr(CO)_5$ (see ESI,† Table 1). In particular, the air-stable tricarbonyl Mn-complex $MnBr(CO)_3(MeCN)_2$ [9] performed exceptionally well, with **3aa** being formed in 98% yield (Table 1, entry 1). Upon testing the current state-of-the-art $MnBr(CO)_5$ complex (entry 2) we found that only trace product formation occurred, supporting our hypothesis that Mn-tricarbonyl complexes would exhibit superior catalytic activity. On the other hand, $[Mn(CO)_3(MeCN)_3]PF_6$, where the Br-ligand is replaced with a non-coordinating PF_6^-, led to lower reactivity (entry 3). When the reaction temperature was lowered to 25 °C the product was delivered in a respectable 50% yield (entry 4). Lowering the catalyst loading had a small appreciable impact (entry 5), with **3aa** being formed in 70% yield. Remarkably, the reaction can be run even with only 2.5 mol% catalyst by raising the temperature to 100 °C (entry 6), affording a 70% yield of **3aa**. To the best of our knowledge, this is the lowest catalyst loading reported for a Mn-catalysed acrylate hydroarylation. A brief survey of ethereal solvents (entries 7–9) revealed that both iPr_2O, THF and 1,4-dioxane performed poorly when compared with Et_2O. Following this, an additive screen (entries 10–11) revealed Cy_2NH to perform significantly better than Et_3N and KOAc. The use of Cy_2NH has been studied extensively in these catalytic manifolds by the groups of Fairlamb and Wang and has been shown to have a positive effect on Mn-catalysed hydroarylation processes.[4d,5,10]

Table 1 Optimisation of reaction. Yields determined by GC-FID using hexadecane as an internal standard

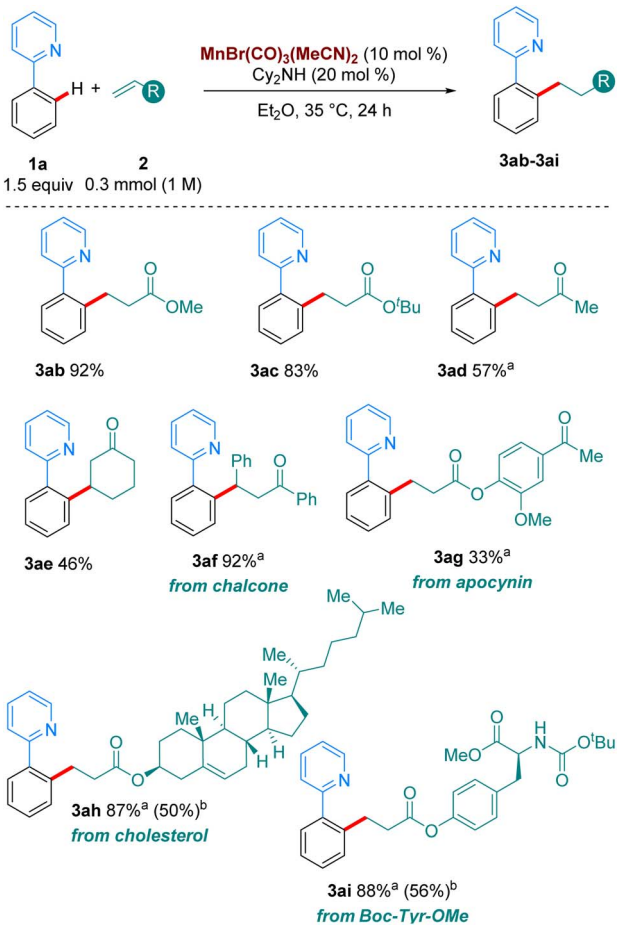
Entry	Variation from standard conditions	**3aa** (%)
1	—	98
2	$MnBr(CO)_5$ (10 mol%) as cat	Trace
3	$[Mn(CO)_3(MeCN)_3]PF_6$ (10 mol%) as cat	51
4	25 °C instead of 35 °C	50
5	5 mol% $MnBr(CO)_3(MeCN)_2$	70
6	2.5 mol% $MnBr(CO)_3(MeCN)_2$ at 100 °C	70
7	iPr_2O as solvent	62
8	THF as solvent	57
9	1,4-Dioxane as solvent	72
10	Et_3N (20 mol%) as additive	44
11	KOAc (20 mol%) as additive	Trace



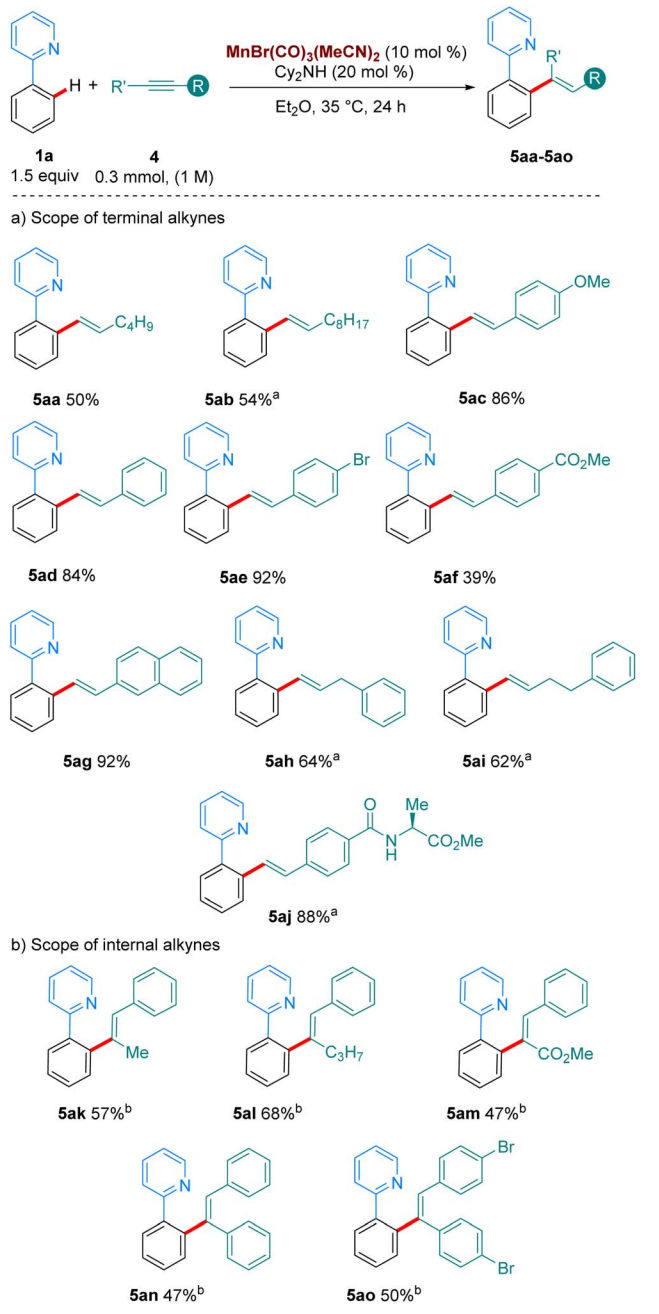
Scheme 2 Scope of the hydroarylation of **2a** with arenes. All yields are of isolated pure compound. [a] The reaction was carried out for 72 h instead of 24 h. [b] With **1o** (0.2 mmol), **2a** (2 equiv.), Mn cat (20 mol%), Cy_2NH (20 mol%) in Et_2O. The reaction was stirred at 35 °C for 72 h. [c] Using $MnBr(CO)_5$ as catalyst (10 mol%) with Cy_2NH (20 mol%) at 100 °C in Bu_2O (0.5 M).

With our optimised reaction conditions in hand, we turned our attention to examining the scope of the reaction (Scheme 2). Pleasingly, the reaction performed well with electron-donating (**3ba**), neutral (**3ca**) and electron withdrawing substituents (**3da-3ga**) at the *para* position of the aromatic ring. Electron-donating and withdrawing substituents were also tolerated at the *ortho* position (**3ha-3ia**). Lower reactivity was observed when these substituents were at the *meta* position (**3ja-3la**). Synthetically relevant pyrazoles and diazepines (imines) were shown to be competent directing groups, with **3na** and **3oa** being formed in good yields. Diazepam, an anxiolytic drug, was successfully late-stage alkylated, with **3pa** being formed in excellent yield and selectivity.

Next, we turned our attention to the scope in alkene coupling partner (Scheme 3). We found that in our optimised reaction conditions, several olefins could react to form the corresponding alkylated products. Acyclic α,β-unsaturated ketone **2d** gave **3ad** in respectable yields. Interestingly, internal olefins, both cyclic and acyclic, also reacted well, with **3ae** and **3af** delivered in 46 and 92% yield, respectively. However, in line with most of the high temperature versions of this method,[4] only electron-deficient olefins are suitable partners. When the alkene coupling partners were electron-rich, only trace amounts of product could be detected. Complex olefins **2g**, **2h** and **2i**, derived from apocynin, cholesterol and Boc-Tyr-OMe, respectively, reacted in our system in moderate to excellent yields, with **3ag**, **3ah** and **3ai** formed in 33%, 87% and 88%, respectively. Importantly, when we carried out the reactions of **1o**, and **1p** with **2a**, as well as those of **1a** with **2h** and **2i** using $MnBr(CO)_5$ at 100 °C much lower yields were obtained of the corresponding



Scheme 3 Scope of the hydroarylation of olefins with **1a**. All yields are of isolated pure compound. [a] The reaction was carried out for 72 h instead of 24 h. [b]Using $MnBr(CO)_5$ as catalyst (10 mol%) with Cy_2NH (20 mol%) at 100 °C in Bu_2O.



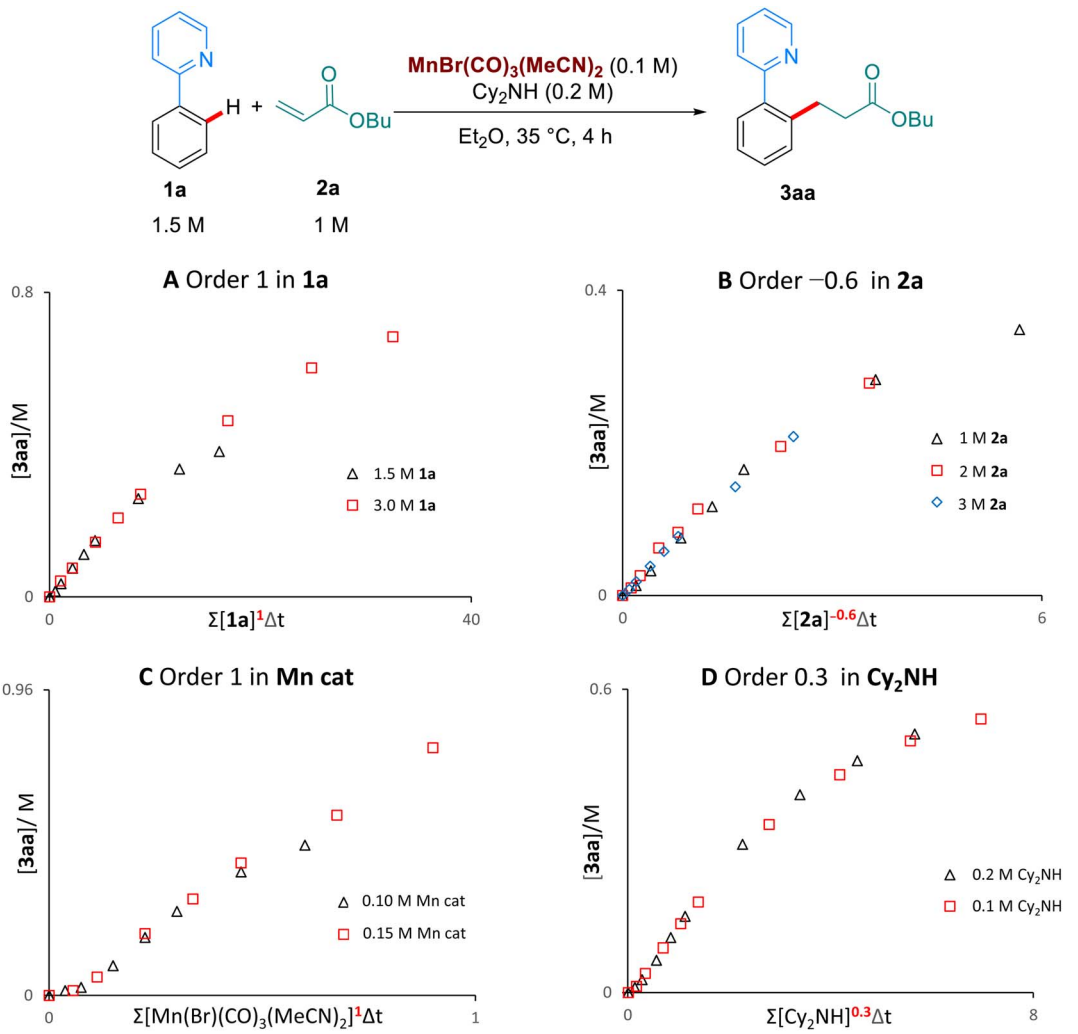
Scheme 4 Scope of the hydroarylation of alkynes with **1a**. All yields are of isolated pure compound. [a] The reaction was carried out for 72 h instead of 24 h. [b] With **1a** (0.3 mmol), **4k-o** (1.5 equiv.), Mn cat (10 mol%), Cy_2NH (30 mol%) and 4-CF_3-benzoic acid (20 mol%) in Et_2O. The reaction was stirred at 35 °C for 72 h.

products, **3oa**, **3pa**, **3ah** and **3ai**. These results emphasize the synthetic advantage provided by the use of the $MnBr(CO)_3(MeCN)_2$ at moderate temperatures.

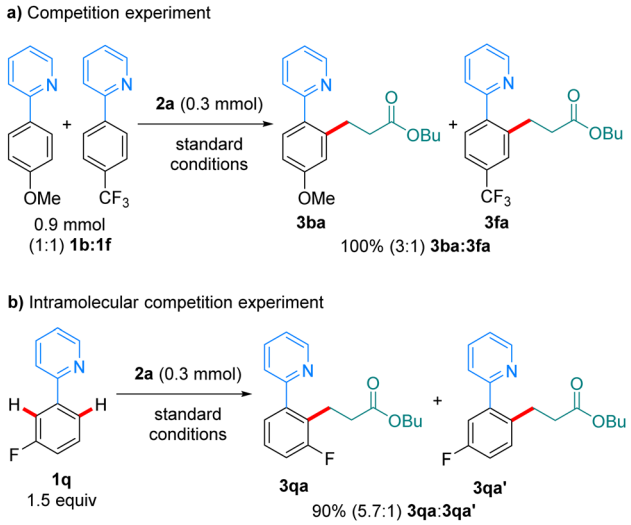
We then turned our attention to the hydroarylation of alkynes with our Mn(I)-tricarbonyl catalyst (Scheme 4). Gratifyingly, aliphatic and aromatic terminal alkynes also reacted well at 35 °C (**5aa–5af**, Scheme 4a), showcasing the superior catalytic activity of manganese tricarbonyl complexes over the classic $MnBr(CO)_5$ complex with functional groups such as OMe, Br, esters, amides and amino acids tolerated in the reaction. Finally, internal alkynes were examined as coupling partners in the reaction (Scheme 4b). Previous work by the group of Fairlamb notes that these substrates have proven to be unproductive in the absence of an acidic additive, due to the favoured protonation of the organometallic intermediate rather than reductive elimination to yield the alkenylated products.[6a,9] We were pleased to find that with the addition of 20 mol% of 4-CF_3-benzoic acid we could access the products of these reactions in good yields also at 35 °C. Unsymmetrical alkynes bearing aryl/alkyl or aryl/carboxymethyl led to completely regioselective addition, forming **5ak–5am**.

We then examined the kinetic orders of the reaction components, in the reaction of **1a** with **2a**, using the VTNA method developed by Burés[11] (Scheme 5). These studies revealed first order kinetics on the Mn-catalyst and on **1a**, as well as a partial order of 0.3 on Cy_2NH. Interestingly, we observed a significantly slower reaction when increasing the concentration of the butyl acrylate substrate **2a**, corresponding to an inverse order of −0.6. To the best of our knowledge this inverse dependence on the concentration of alkene has never been observed in the Mn-catalysed hydroarylation of olefins, and suggests that multiple coordinations of the alkene are possible to form an off-cycle species of the type $[Mn(\mathbf{2a})_2]$. Lynam and Fairlamb have previously shown that **2a** can coordinate to Mn through both oxygen and the olefin.[6b]

In a competition experiment between **1b** and **1f** in their reaction with **2a** (scheme 6a), the more electron-rich arene reacted preferentially, with **3ba** being formed over **3fa** in a 3 : 1 ratio. This could be explained by preferential coordination to the Mn-catalyst of the more electron-rich **1b**. An intramolecular competition experiment using substrate **1q** showed preferential reaction on the most acidic C–H bond (Scheme 6b). The



Scheme 5 Kinetic analysis by VTNA.



Scheme 6 Competition experiments.

observed regioselectivity (5.7 : 1) closely resembles that recently reported by Lynam and Fairlamb on the hydroarylation of **1q** with phenylacetylene,[12,13] and suggests that the C–H activation step is irreversible under the reaction conditions.

Conclusions

We have demonstrated that $MnBr(CO)_3(MeCN)_2$ is a highly active catalyst for the hydroarylation of electron-deficient olefins, and of terminal and internal alkynes. This procedure has a broad functional group tolerance, owing to the mild conditions enabled by the catalyst. This method has been applied to the late-stage diversification and functionalisation of natural products and pharmaceutical molecules, displaying its synthetic utility potential. Preliminary mechanistic studies suggest that the C–H activation step is irreversible and that high concentrations of the alkene coupling partner have a deleterious effect on reactivity. The high reactivity of Mn-tricarbonyl complexes compared to $MnBr(CO)_5$, is attributed to the prevention of formation of $Mn(CO)_4$-species, previously proposed as an off-cycle catalyst sink. The exploration of further applications of this new Mn-catalyst are under way.

Data availability

All experimental procedures and compound characterization can be found in the ESI.†

Author contributions

D. M. C. conceived the project and carried out initial discovery work and optimisation. S. C. isolated and characterised all compounds and contributed to the optimisation of the reaction. M. W. assisted S. C. with the running of the project and compound isolation. I. L. secured the funding used in this study and directed the work. M. W. and I. L. prepared the manuscript with input from S. C.

Conflicts of interest

There are no conflicts to declare.

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