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C–H Activation

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Manganese(I)-Catalyzed C–H Activation: The Key Role of a 7-Membered Manganacycle in H-Transfer and Reductive Elimination

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Dedicated to Professors Michael Bruce and Robin N. Perutz

Abstract: Manganese-catalyzed C–H bond activation chemistry is emerging as a powerful and complementary method for molecular functionalization. A highly reactive seven-membered Mn^I intermediate is detected and characterized that is effective for H-transfer or reductive elimination to deliver alkenylated or pyridinium products, respectively. The two pathways are determined at Mn^I by judicious choice of an electron-deficient 2-pyrone substrate containing a 2-pyridyl directing group, which undergoes regioselective C–H bond activation, serving as a valuable system for probing the mechanistic features of Mn C–H bond activation chemistry.

C–H bond activation–functionalization chemistry is a central arena for catalyst development and synthetic application.^[1] Transition metals mediate the efficient and selective activation of C–H bonds, with recent attention focusing on environmentally benign and sustainable metals, for example, Mn, Co, Fe, and Cu.^[2] Mn^I promotes C–H activation of substrates containing nitrogen-directing groups.^[3] For example, **1** gives cyclomanganated complex **2**, with subsequent reaction with alkyne **3** forming a proposed 7-membered ring intermediate **4** (Scheme 1).^[4] Formation of either **5**, **6**, or **7** results from reductive elimination, H-transfer, or dehydrogenative annulation, respectively.

Processes utilizing Mn^I, particularly [Mn(C[^]N)(CO)₄]**2**,^[5,6] have been of broad interest. The mechanistic features of the remarkable synthetic work of Ackermann and Wang,^[3,4] where intermediates **4a–c** have been proposed,

prompted us to examine whether they could be detected and characterized and then subsequently be shown to deliver organic products such as **5–7**. Complexes **4d–f**, formed by insertion of internal alkynes are known,^[6,7] but their competence in terms of a fully connected reaction system, affording organic products, has not been examined. As 18-electron species containing four CO ligands, possessing high thermodynamic stability, they are unlikely to be directly involved in the catalytic cycle.^[8]

Herein we describe a suitable reaction system (**1g**→**4g**→**5g** or **6g**, Scheme 1) that takes advantage of the exquisite reactivity of an electron-deficient 2-pyrone ring system containing a 2-pyridyl directing group (**1g**). We recognized that the 2-pyrone could act as a hemilabile ligand in 7-membered manganacycle **4g**, potentially providing sufficient stabilisation for observation of this key intermediate. Our findings demonstrate that **4g** acts as a central manifold to reductive elimination and H-transfer, giving products **5g** and **6g**, respectively, with details described herein.

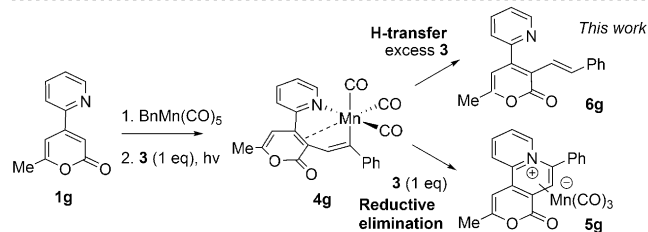
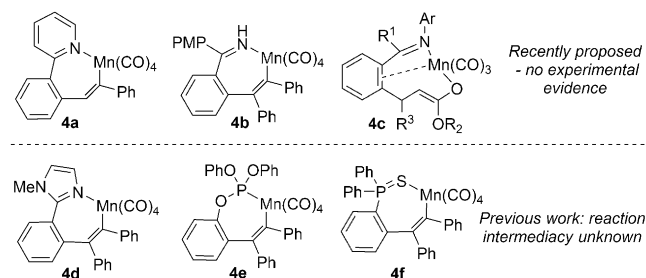
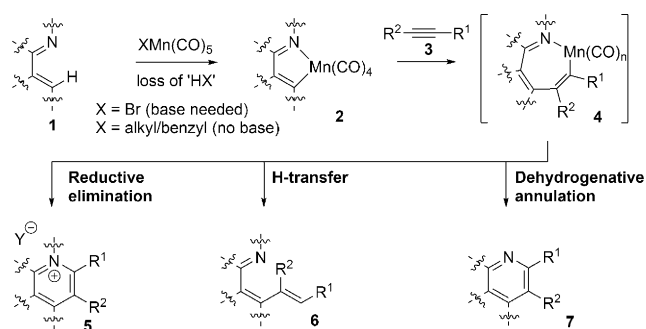
Our study began with the reaction of 2-pyrone **1g** with BnMn(CO)₅ in hexane at 75 °C, which gave cyclometalated **2g** cleanly and in quantitative yield (Scheme 2). Complex **2g** was fully characterized (see the Supporting Information); a single crystal X-ray structure confirmed that regioselective C–H activation occurred at C3, in keeping with Pd^{II}-direct arylations of 2-pyrones,^[9] albeit most likely by a σ-CAM-type process.^[10]

We hypothesized that UV irradiation^[11] of **2g** would lead to solvated intermediate **I_{pyr}** (Scheme 2, middle inset).^[12] Subsequent alkyne trapping via intermediate **II_{pyr}**, would then convert into the alkyne insertion manganacycle **4g**. UV irradiation (Hg/Xe Arc lamp, 200–2500 nm) of a mixture of **2g** and **3** (1.1 equiv) in [D₈]THF at 240 K (at 5 min intervals), and reaction monitoring by ¹H NMR spectroscopy between intervals, revealed the formation of a new intermediate that grows up to 9.6 % conversion. Further irradiation resulted in spectral broadening (paramagnetic species), but crucially, full NMR analysis of manganacycle **4g** was possible, with HMQC/HMBC correlation methods/n.O.e. experiments. Analysis shows that **4g** formed regioselectively at C3 (Scheme 2, bottom inset). MS analysis also confirmed the presence of **4g** (LIFDI *m/z* 427 for [M]⁺ and ESI *m/z* 428 for [MH]⁺) in solution.

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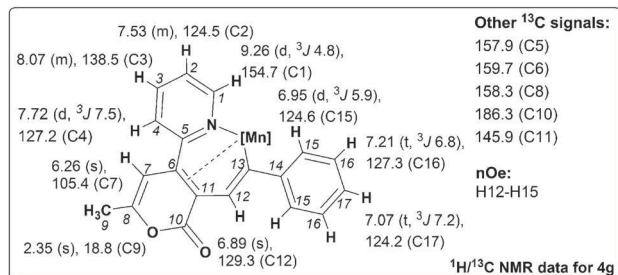
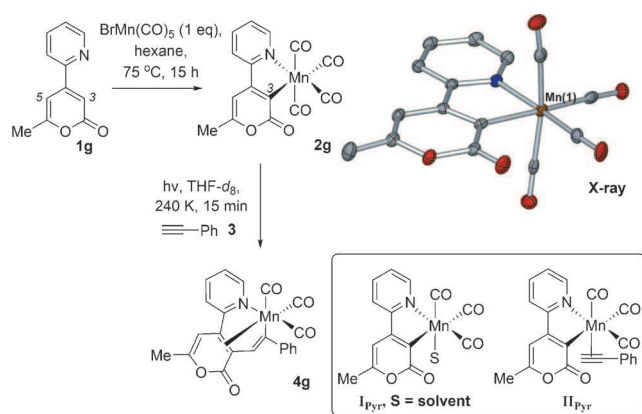


Scheme 1. Manganese(I)-catalyzed C–H activation, and potential products and intermediates.

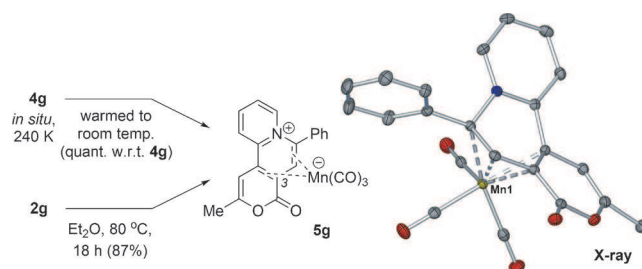
Experimentally there is evidence in **4g** of an interaction between the 2-pyrone olefinic bond (C6–C11) and the Mn^I center at $\delta = 159.7$ ppm (C6) and $\delta = 145.9$ ppm (C11), which stabilizes the tricarbonyl complex. Computational studies (DFT methods) confirm that HOMO–4 within **4g** has 2-pyrone–Mn bonding character (see the Supporting Information), confirming **4g** as a feasible structure. The small coordination shifts in the ¹³C{¹H} NMR spectrum imply this interaction is weak, although generation of a vacant site at Mn (**4g'**) and subsequent alkyne coordination (**4g''**) ought to be feasible. The DFT studies for **III_{Pyr}** (**4g**) and **III_{Ph}** (**4a**) indicate no low-lying vacant orbitals (HOMO–LUMO gap = 1.70154–1.97588 eV), consistent with Mn having an 18-electron count.

Warming of the [D₈]THF solution of **4g** to room temperature led to the formation of the reductive elimination product **5g** (Scheme 3). Complex **5g** was fully characterized (see the Supporting Information) and confirmed by X-ray analysis to possess a Mn(CO)₃ anion. **5g** was also formed in 87% yield on treatment of **2g** with **3** (1.1 equiv.) at 80 °C, Et₂O, 18 h (sealed tube). Thus, the same reaction pathway (**2g** + **3** → **5g**) results from either UV irradiation or thermal heating, validating our approach in utilizing UV irradiation to enable detection and characterization of intermediate **4g**.

Interestingly, catalytic reactions of **1g** with **3**, under the reaction conditions reported by Wang et al.^[4] for 2-phenyl-

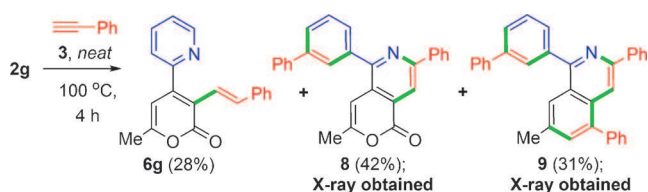


Scheme 2. Cyclomanganation of **1g** gives **2g**, which upon photolysis with phenylacetylene **3** gives **4g**. The X-ray structure of **2g** is given (top right, ellipsoids set at 50% probability; H-atoms omitted and Mn atom labeled only for clarity). Insets: proposed transient intermediates on route to **4g** and the key NMR data for **4g**.



Scheme 3. Thermally controlled reductive elimination from either **2g** or **4g** to give **5g**. An X-ray structure of a single crystal of **5g** is also shown (ellipsoids set to 50% probability; H-atoms omitted and Mn atom labeled only, for clarity).

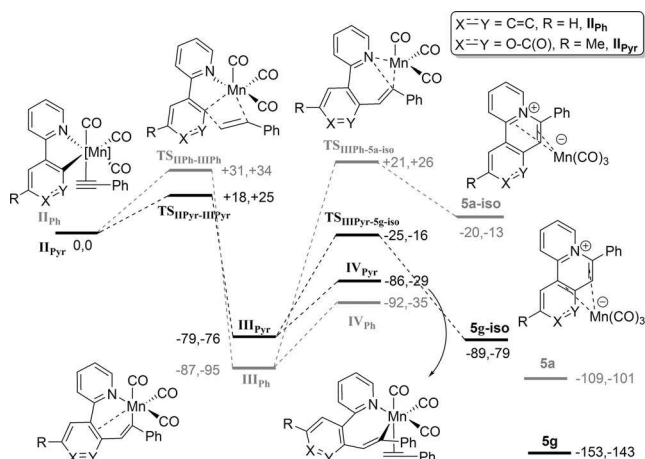
pyridine **1a** (conditions: BrMn(CO)₅, C₂NH, Et₂O, 100 °C for 6–24 h), do not lead to formation of alkenylated products (for example, **6g**). This indicates that the rate of reductive elimination from **4g** to give **5g** is faster than the rate for alkyne H-transfer to give **6g** (see above). We rationalized that reaction of **2g** in neat phenylacetylene **3** would enable H-transfer to become the dominant pathway (Scheme 4), but the reaction afforded three new products. Firstly, the H-transfer product **6g** was formed in 28% yield; an excess of **3** favors H-transfer over reductive elimination. Central to the success of the reaction is coordination of a second molecule of alkyne **3** and subsequent alkyne H-transfer of intermediate **4g**. The other products **8** and **9** were unexpected, resulting from a noteworthy Diels–Alder reaction (DAR) of **3** with the 2-pyridine ring,^[13] followed by ring fragmentation (single-



Scheme 4. Reaction of **2g** in neat phenylacetylene **3**. The green bonds show the newly formed bonds in the organic products, with red showing the insertion location of **3** (**5g** not observed under these reaction conditions).

crystal X-ray structures of **8** and **9** confirmed the molecular connectivity, correlating with NMR spectroscopy, see the Supporting Information). Compound **9** shows that the 2-pyrone participated in a secondary inverse electron demand DAR.^[14] Along with **6g**, both **8** and **9** derive from **4g**, where the DARs and 2-pyridyl fragmentation are secondary reactions.

To understand the steps leading to the formation of **5g** DFT methods were used (Scheme 5, see the Supporting



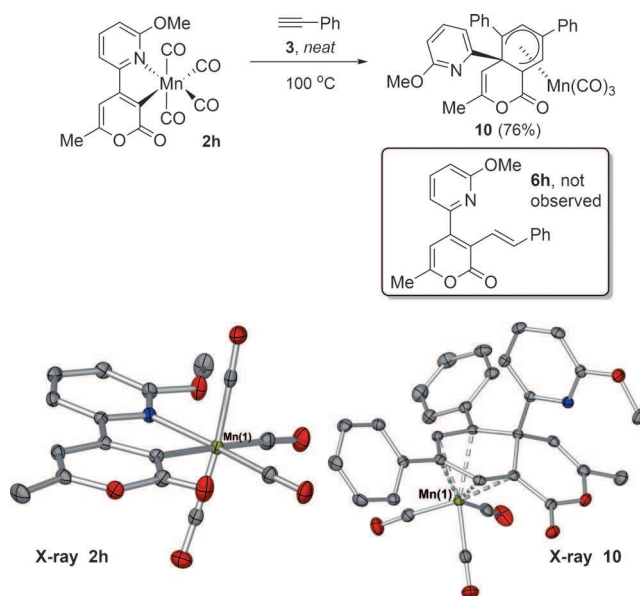
Scheme 5. DFT calculations showing the feasibility of reductive elimination from **5a** and **5g**, starting from intermediates **II_{ph}** and **II_{pyr}** respectively. Energies are zero point energy-corrected electronic energies and Gibbs energies at 298.15 K in kJ mol^{-1} relative to **II**.

Information for details of DFT calculations). Starting from **II_{pyr}**, formed via loss of CO from **2g** and coordination of **3**, insertion of coordinated alkyne into the Mn–C(pyrone) bond proceeds through a low-energy transition state (**TS_{IIpyr-IIpyr}**) to give **III_{pyr}**. The latter intermediate is equivalent to characterized **4g**. C–N reductive elimination from **III_{pyr}** via transition state **TS_{IIIpyr-5g-iso}**, results in the formation of the 2-methyl-4-oxo-6-phenyl-4*H*-3,7λ⁵-pyrano[4,3-*a*]quinolizin-7-ylum ring system (**5g**). A DRC analysis of **TS_{IIIpyr-5g-iso}** revealed that the imaginary eigenvector led to **5g-iso** (the coordination isomer of **5g**); a π -slip then gives **5g**.

The corresponding potential energy surface for the phenyl-substituted system (giving the Chen and Wang product **5a**) revealed that the same reaction pathway was viable (pathway shown in gray in Scheme 5). The barrier to insertion of **3** (**TS_{II-III}**) was slightly greater (Gibbs energies at 298.15 K

relative to the respective compound **II** + 25 kJ mol^{-1} for 2-pyrone versus + 34 kJ mol^{-1} for phenyl) and that **III_{pyr}** was relatively higher in energy than **III_{ph}** (–76 kJ mol^{-1} versus –95 kJ mol^{-1}). To explain the different outcome from the phenyl and 2-pyrone substituents it is informative to consider the higher energy of **TS_{IIIph-5a-iso}** (+ 26 kJ mol^{-1}) against **TS_{IIIpyr-5g-iso}** (–16 kJ mol^{-1}). Therefore, the energetic spans for reductive elimination are 60 kJ mol^{-1} (2-pyrone) and 121 kJ mol^{-1} (phenyl). When compared with the formation of **IV_{pyr}** and **IV_{ph}**, which is the next step in forming H-transfer products **5g** and **5a**, respectively, it is evident that the reductive elimination to form **5g** is competitive, but in the case of **5a** the much larger energetic span to reductive elimination allows for productive catalysis via alkyne coordination to give **IV_{ph}**.^[4]

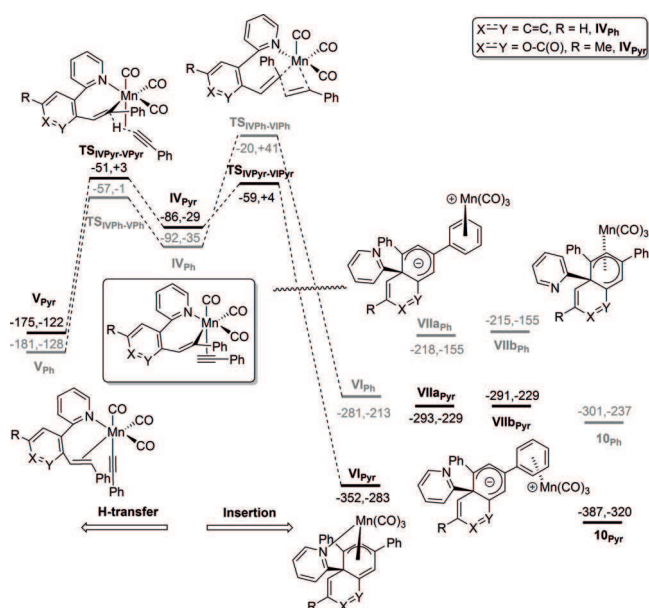
While no double alkyne insertion products were detected in reactions of **2g** with phenylacetylene **3**, the reaction of related derivative **2h** with **3** resulted in exclusive formation of double alkyne insertion product **10** (Scheme 6; the structure



Scheme 6. Double alkyne insertion into **2h**. Dotted lines show Mn coordination in complex **10** for clarity (ellipsoids set to 50% probability; H-atoms omitted and Mn atom labeled only, for clarity).

of **6h** is shown as an expected alkenylated product). This remarkable result shows the impact that a subtle change to the pyridyl directing group has on the barriers to these steps.

We rationalized the experimental observations by DFT calculations, which enabled a mechanism for this reaction and the differences between the phenyl- and 2-pyrone-substituted complexes to be proposed (Scheme 7). In the case of the pyrone derivative, coordination of alkyne to **III_{pyr}** results in formation of **IV_{pyr}** having two energetically accessible fates. H-transfer through **TS_{IVpyr-Vpyr}** (+ 3 kJ mol^{-1}) results in the formation of alkynyl complex **V_{pyr}** which would liberate **6h**, however insertion of the alkyne into the Mn–C bond of **IV_{pyr}** through **TS_{IVpyr-VIpyr}** (+ 4 kJ mol^{-1}) affords more energetically favourable **VI_{pyr}**. The process seen for reactions of **2h** has



Scheme 7. DFT calculations showing the feasibility of a double alkyne insertion pathway to rationalize formation of double alkyne insertion product **10**. Energies are zero point energy-corrected electronic energies and Gibbs energies at 298.15 K in kJ mol^{-1} relative to **II**.^[17]

resulted in the formation of two C–C bonds. Preliminary investigations indicate that this proceeds through a “two-steps no intermediate” pathway^[15] with the initial insertion into the Mn–C bond, followed by cyclization giving a six-membered ring without an intermediate. However, in **VI**_{pyr} the Mn is η^3 -coordinated to the pendant pyridyl group and newly formed ring. To form **10**_{pyr}, which is the lowest point on the potential energy surface at -320 kJ mol^{-1} , the Mn needs to migrate to the alternative ring-face. We postulate that this involves migration onto one of the phenyl rings in the ligand, for example, **VIIa**_{pyr}. The ring rotates allowing the Mn to migrate to the other face of the pentadienyl system, giving **VIIb**_{pyr}. It is reasonable to presume that this proceeds via a low energy ring-walking process.^[16]

In the case of the phenyl derivative, all of the states predicted for the 2-pyrone system are viable; however, **TS**_{IVPh-VPh} is far higher in energy than **TS**_{IVPh-VPh} ($+41 \text{ kJ mol}^{-1}$ versus -1 kJ mol^{-1}). Therefore, insertion of the second alkyne is non-competitive, with the H-transfer pathway leading to the alkenylated product, consistent with experimental observations.

In conclusion, we have detected and characterized a commonly proposed 7-membered manganese cycle **4g** (of direct relevance to generic structure **4**, Scheme 1). Manganese cycle **4g** sits at the selectivity junction to reductive elimination or H-transfer steps. Depending on the reaction conditions, **5g** or **6g** products form that correspond to reductive elimination and protonation pathways, respectively. Double alkyne insertion to give **10** has also been revealed in these studies. Our observations provide the first clear cut evidence that manganese cycles such as **4** are key intermediates in Mn^I-mediated C–H bond activation processes involving substrates containing directing groups.^[3,4,7] More generally, such intermediates

may be considered as leading to side reactions, but here we have shown that it presents an opportunity to control product selectivity. Serendipitously we have uncovered a rare example of a DAR of a pyridine derivative, where the intermediate fragments to form products such as **8** and **9**. Taken together, our findings provide a unique insight into Mn^I-mediated C–H bond activation processes, especially how relatively minor changes in substrate structure influence product selection; Mn^I-based metallocycles clearly offer rich chemistry,^[3] much potential, and warrant further study more generally in organic and organometallic chemistry.

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