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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 MnI intermediate is detected and characterized that is effective for H-transfer or reductive elimination to deliver allenylated or pyrydinium products, respectively. The two pathways are determined at MnI 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. 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. Mn(I) promotes C–H activation of substrates containing nitrogen-directing groups. For example, 1 gives cyclometalated complex 2, with subsequent reaction with alkene 3 forming a proposed 7-membered ring intermediate 4 (Scheme 1). Formation of either 5, 6, or 7 results from reductive elimination, H-transfer, or dehydrogenative annihilation, respectively. Processes utilizing Mn(I), particularly [Mn(C^N)(CO)_4], have been of broad interest. The mechanistic features of the remarkable synthetic work of Ackermann and Wang, where intermediates 4a–e 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, 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.

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-pyrene ring system containing a 2-pyridyl directing group (1g). We recognized that the 2-pyrene 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-pyrene 1g with BnMn(CO)_4 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(I)-direct arylation of 2-pyrone,[12] albeit most likely by a β-CAM-type process.[13]

We hypothesized that UV irradiation of 2g would lead to solvated intermediate 1 pry, (Scheme 2, middle inset). Subsequent alkyn trapping via intermediate H pry would then convert into the alkyn insertion manganacycle 4g. UV irradiation (Hg/Xe Arc lamp, 200–2500 nm) of a mixture of 2g and 3 (1.1 equiv) in [D_8]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/ HMQC 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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Experimentally there is evidence in 4g of an interaction between the 2-pyrone olefinic bond (C6-C11) and the Mn1 center at δ = 159.7 ppm (C6) and δ = 145.9 ppm (C11), which stabilizes the tricarbonyl complex. Computational studies (DFT methods) confirm that HOMO/C0 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 P (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)5 anion. 5g was also formed in 87% yield on treatment of 4g 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. for 2-phenylpyridine 1a (conditions: BrMn(CO)5, CyNH, 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 E followed by ring fragmentation (single-
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-pyryl participated in a secondary inverse electron demand DAR. 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 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 (TSII-Pyr-IIIPyr) to give IIIPyr. The latter intermediate is equivalent to characterized 4g. C–N reductive elimination from IIIPyr via transition state TSIIIPyr-5g-isoo results in the formation of the 2-methyl-4-oxo-6-phenyl-4H-3,7,8-pyran-4-ylidene[4,3-a]quinolizin-7-ylidene ring system (5g). A DRC analysis of TSIIIPyr-5g-isoo revealed that the imaginary eigenvector led to 5g-isoo (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 (TSIII-H) was slightly greater (Gibbs energies at 298.15 K relative to the respective compound II + 25 kJ mol⁻¹ for 2-pyryl versus +34 kJ mol⁻¹ for phenyl) and that III-Pyr was relatively higher in energy than III-Pyr (-76 kJ mol⁻¹ versus -95 kJ mol⁻¹). To explain the different outcome from the phenyl and 2-pyryl substituents it is informative to consider the higher energy of TSIIIPyr-5g-isoo (+26 kJ mol⁻¹) against TSIIIPyr-5g iso (-16 kJ mol⁻¹). Therefore, the energetic spans for reductive elimination are 60 kJ mol⁻¹ (2-pyryl) and 121 kJ mol⁻¹ (phenyl). When compared with the formation of IV-Pyr and IV-Pyr, 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-Pyr.

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...
resulted in the formation of two C–C bonds. Preliminary investigations indicate that this proceeds through a “two-steps no intermediate” pathway with the initial insertion into the Mn–C bond, followed by cyclization giving a six-membered ring without an intermediate. However, in VIa, the Mn is {\(\eta^2\)}-coordinated to the pendant pyridyl group and newly formed ring. To form X, 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. The ring rotates allowing the Mn to migrate to the other face of the pentadienyl system, giving VIIb. It is reasonable to presume that this proceeds via a low energy ring-walking process.

In the case of the phenyl derivative, all of the states predicted for the 2-pyrone system are viable; however, TS in the pyridyl-phenyl twisted system is far higher in energy than TS in the pyridyl-phenyl twisted system (−41 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 manganacycle \(4g\) (of direct relevance to generic structure 4, Scheme 1). Manganacycle \(4g\) 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 clearcut evidence that manganacycles such as 4 are key intermediates in Mn\(^{2+}\)-mediated C–H bond activation processes involving substrates containing directing groups. 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\(^{2+}\)-mediated C–H bond activation processes, especially how relatively minor changes in substrate structure influence product selection; Mn\(^{2+}\)-based metallocycles clearly offer rich chemistry, much potential, and warrant further study more generally in organic and organometallic chemistry.

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