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Mechanistic Study of the Manganese-Catalyzed [2 + 2 + 2] Annulation of 1,3-Dicarbonyl Compounds and Terminal Alkynes

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Abstract: The manganese-catalyzed dehydrative [2 + 2 + 2] annulation reaction of a 1,3-dicarbonyl compound and a terminal alkyne provides an efficient and regioselective synthesis of a substituted benzene derivative, highlighted by the exclusive formation of a *p*-terphenyl derivative from an aryl acetylene. The mechanism and the origin of the regioselectivity of the reaction were explored by experiments and density functional theory (DFT) calculations. Experimental data revealed the cis stereochemistry of a cyclohexadienol precursor to the benzene product and suggested that two reaction pathways may operate competitively—sequential carbometalation reactions of a manganese enolate and formation of a manganacyclopentadiene intermediate. The DFT study supported the first possibility, namely that the reaction involves three steps: (1) addition of a manganese enolate of a 1,3-dicarbonyl compound to a terminal alkyne to give a vinylmanganese complex, (2) insertion of a second alkyne into the vinyl−Mn bond to give a dienylmanganese complex, and (3) intramolecular nucleophilic addition of the dienylmanganese to the carbonyl group. This mechanism is consistent with the experimental facts such as the perfect regioselectivity of the reaction of an aryl acetylene, the moderate regioselectivity of the reaction of an alkyl acetylene, and the stereochemistry of the annulation product. An alternative mechanism involving a manganacyclopentadiene intermediate failed to account for the experimental regioselectivity, although it may be occurring as a very minor competitive pathway.

Introduction

Transition metal-catalyzed [2 + 2 + 2] cyclotrimerization of alkynes (eq 1) provides a classical, reliable, and straightforward synthetic entry to substituted arenes and has been extensively studied since the discovery of nickel-catalyzed reactions by Reppe et al. in 1948.[1−3] The reactions are considered to involve a metallacyclopentadiene intermediate formed through oxidative cyclization of two alkynes.[4] A new [2 + 2 + 2] synthetic route to arenes was reported recently by us[5] and others.[6] It is a Mn-catalyzed coupling of a 1,3-dicarbonyl compound and 2 mol of an alkyne, which produces *p*-terphenyl derivatives **1** with perfect regioselectivity from an aryl acetylene (Scheme 1a). The reaction first generates a *cis*-cyclohexadienol intermediate **2** as an exclusive stereo- and regioisomer (as reported below), which is dehydrated in situ to give the single regioisomeric product **1** and water. An alkyl acetylene exhibits similar but lower regioselectivity (Scheme 1b). Thus, 1-octyne or 3-phenylpropyne reacts with ethyl benzoylacetate to give para and meta isomers (***p*-3** and ***m*1-3**) in ca. 3:1 ratio. None of the other possible meta and ortho isomers (***m*2-3** and ***o*-3**) was formed. The reaction is sensitive to the steric hindrance of the

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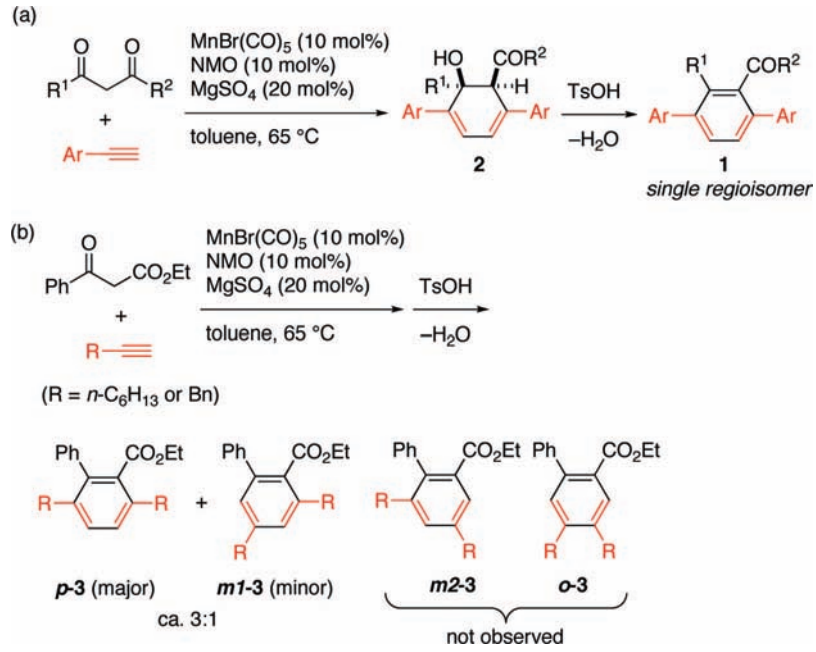
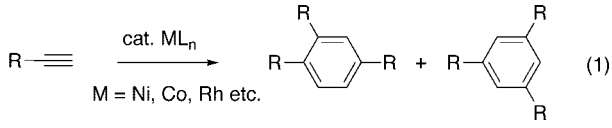
Scheme 1. Mn-Catalyzed [2 + 2 + 2] Annulation of a 1,3-Dicarbonyl Compound and a Terminal Alkyne (refs 5 and 6)

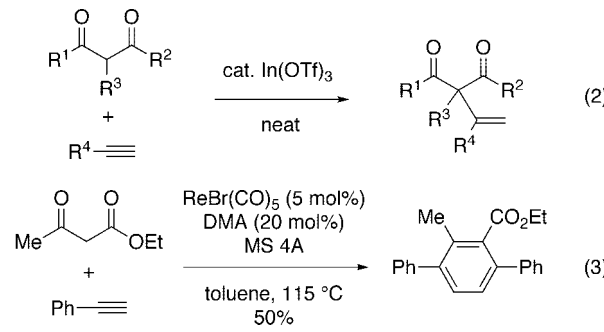


substituents on the dicarbonyl compound and the alkyne. In addition, cyclic 1,3-diketones do not take part in the reaction at all.



(1)

The catalyst system may be either $MnBr(CO)_5$, *N*-methylmorpholine *N*-oxide (NMO), and $MgSO_4$[5] or $MnBr(CO)_5$ and MS 4A.[6] The reaction represents a rare example of a manganese-catalyzed C−C bond formation reaction under neutral conditions.[7,8] The reaction appears to have some mechanistic kinship to the reactions of zinc[9] and indium[10] enolates with alkynes (eq 2), but neither zinc nor indium catalysts exhibit the annulation reactivity. Typical metal carbonyl complexes that we examined ($Mo(CO)_6$,$W(CO)_6$,$FeI_2(CO)_4$,$[RuCl_2(CO)_3]_2$,$Co_2(CO)_8$,Rh(acac)$(CO)_2$, and $IrCl(CO)(PPh_3)_2$) do not show the catalytic activity either; however, $ReBr(CO)_5$ as examined by Kuninobu and Takai showed moderate catalytic activity (eq 3).[6,11]



(2)

(3)

On the basis of the similarity of the reaction to the classical alkyne trimerization (eq 1) and to the metal enolate addition to an alkyne (eq 2), one can consider a priori two mechanistic possibilities (Scheme 2). One involves sequential carbometalation reactions of a manganese enolate of the 1,3-dicarbonyl compound to the alkyne followed by intramolecular carbonyl addition of the organomanganese intermediate (path A),[10] while the other involves a manganacyclopentadiene[12] intermediate (path B).[13] One puzzling aspect of the regioselectivity in path A is that to account for the experimental regioselectivity, the

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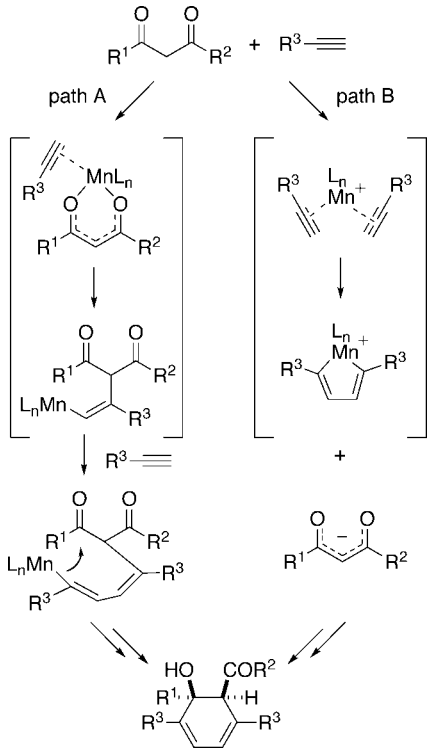
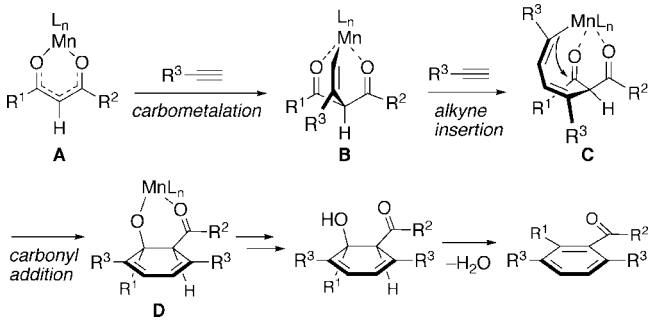
(13) An alternative mechanistic possibility involving manganacyclopentene formation from a 1,3-dicarbonyl compound and acetylene has been suggested by Kuninobu/Takai (ref 6). We briefly studied this possibility, and excluded it because of very high activation energy ($\Delta E^{\ddagger}$ = 30.2 kcal/mol) and endothermicity of the reaction (ΔE = 28.3 kcal/mol). See Scheme S3 for details.

Scheme 2. Two Possible Pathways of Mn-Catalyzed [2 + 2 + 2] Annulation



Scheme 3. Proposed Pathway for Mn-Catalyzed [2 + 2 + 2] Annulation

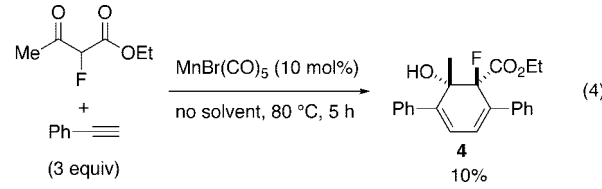


first C−C bond formation must take place at the substituted side of the alkyne and the second one occurs on the other side. Regioselectivity of path B is also problematic since it requires exclusive formation of the symmetric manganacyclopentadiene intermediate.

To examine the mechanistic dichotomy, the origin of the regioselectivity, and the reactivities of organomanganese complexes, we studied the pathways of the Mn-catalyzed [2 + 2 + 2] annulation reaction experimentally and with the aid of density functional theory (DFT) calculations. We propose herein that the reaction takes place via sequential carbometalative reactions; that is, path A (details shown in Scheme 3).

Results and Discussion

We first summarize here some experimental data that are relevant to the present mechanistic discussion. First, we describe the stereochemistry of the [2 + 2 + 2] annulation reaction. Although the cyclohexadienol intermediates **2** in general (Scheme 1a) are not stable enough for unambiguous structural determination, we managed to synthesize, as a single regio- and stereoisomer in 10% yield, the fluorocyclohexadienol product **4** by the reaction of an α-fluoro-β-ketoester and phenylacetylene (3 equiv) in the presence of $MnBr(CO)_5$ (10 mol%) (eq 4). The X-ray diffraction analysis of **4** indicated the cis stereochemistry between the hydroxy and ethoxycarbonyl groups (Figure 1).



Second, we describe a minor reaction reported by Kuninobu and Takai,[6] who noted that the reaction of 2,4-pentanedione with phenylacetylene gives an annulation product **5** (69%) and its deacylated product **6** (5%), along with a small amount of an α-alkenylated product **7** (7%, Scheme 4). The formation of the side product **7** is an indication of the mechanistic kinship between this reaction and the indium-catalyzed reaction (eq 2).

The third reaction is the formation of an acetylene cyclotrimerization side product (Scheme 5). The reaction of ethyl benzoylacetate and 2-methoxyphenylacetylene gave the expected

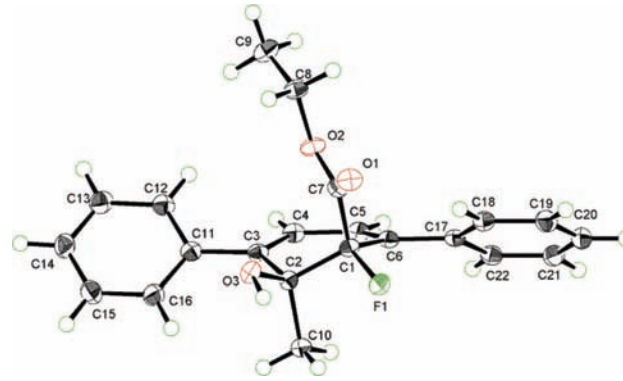
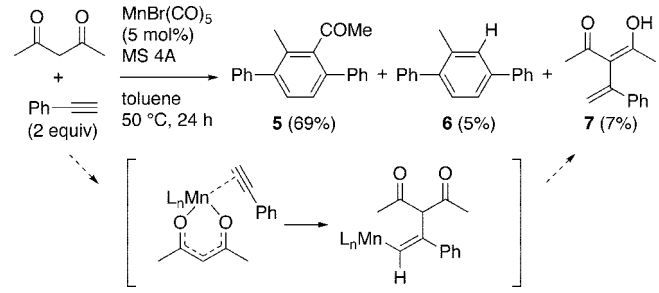
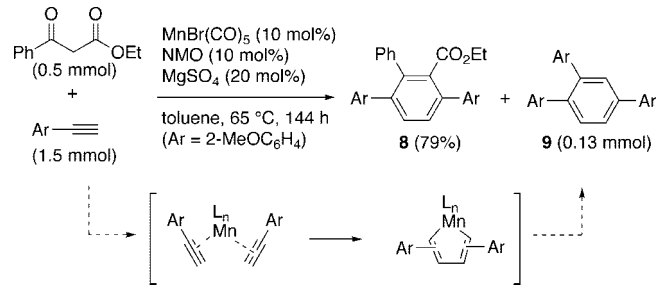


Figure 1. ORTEP drawing of cyclohexadienol **4** (50% probability for thermal ellipsoids).

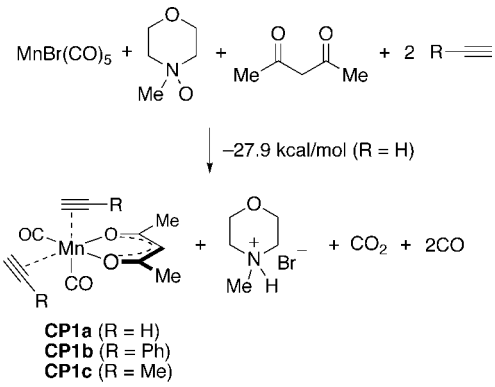
Scheme 4



Scheme 5



Scheme 6

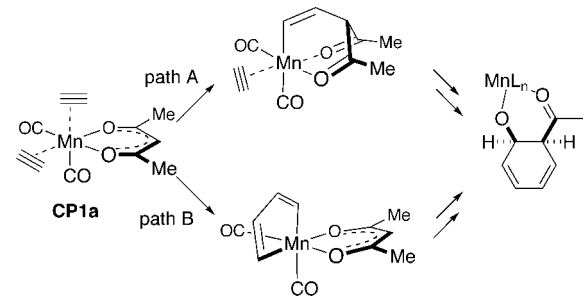


ketoester/alkyne annulation product **8** (79%) accompanied by a small amount of the cyclotrimerization product **9**, suggestive of a competitive reaction involving a metallacyclopentadiene intermediate. When we used acetylene gas, we noted the formation of a trace amount of benzene together with the desired [2 + 2 + 2] cycloadduct in low yield. Interestingly, the acetylene trimerization reaction did not occur in the absence of the ketoester in spite of our substantial effort to establish the generality of the reaction.

Finally, we note the roles of the catalytic additives (i.e., NMO and $MgSO_4$).[5] The addition of NMO significantly accelerates the reaction. Amine *N*-oxides are known to oxidize a CO ligand on a metal carbonyl complex into CO_2,[14] to create a vacant site, and to accelerate the Mn-mediated indene synthesis[15] and the Co-mediated Pauson−Khand reaction.[16] In agreement with such precedents, the present arene synthesis is greatly accelerated by NMO and is significantly retarded under a CO atmosphere. The presence of anhydrous $MgSO_4$ is often beneficial for improving the yield, by removing water and suppressing undesirable side reactions (e.g., one major side product in the absence of $MgSO_4$ that we found resulted from hydrolysis of the ester group in the product).

Computational Models. On the basis of the above experimental information, we reasoned that the [2 + 2 + 2] annulation takes place through either path A or path B (Scheme 2), and we studied two model reactions starting from the same model 18-electron manganese(I) complex **CP1a−c** that bears one acetylacetonate (acac) ligand, two alkyne ligands (acetylene, phenylacetylene, or propyne), and two CO ligands in an octahedral environment (Scheme 6). The formation of complex **CP1a** from one molecule each of $MnBr(CO)_5$, NMO, and acetylacetone, and two molecules of acetylene was calculated to be exothermic by 27.9 kcal/mol. Note that **CP1a** is in the most favorable coordination environment among the geometrical isomers. This coordination environment of **CP1a** is such that either the enolate moiety can add to the acetylene (path A in Scheme 7) or the two acetylene molecules can form a manganacycle (path B). We explored both mechanistic possibilities for the acetylene complex **CP1a** and then replaced the acetylene by phenylacetylene (**CP1b**) or propyne (**CP1c**) to probe the

Scheme 7



regioselectivity of each mechanism. It was found that both pathways are energetically favorable for acetylene and that path A not only becomes energetically favored over path B but also reproduces the experimental selectivity very well when the substituted alkynes are employed.

Because the exact nature of the catalytically active species is unclear at present, we also studied the two pathways for similar Mn complexes possessing different ligand compositions (see Supporting Information for details). Regardless of the initial ligand composition, we have drawn the same conclusion, i.e., the sequential carbometalation pathway reproduces the experimental regioselectivity, while the manganacyclopentadiene pathway does not.[17]

Computational Methods. All calculations were performed with the Gaussian 03 suite of programs.[18] The DFT method was employed using the B3LYP hybrid functional.[19] Geometry optimization was performed with a basis set (denoted as 631LAN) consisting of the LANL2DZ basis set including a double-ζ valence basis set with the Hay and Wadt effective core potential (ECP) for Mn[20] and 6-31G(d) basis set for the rest.[21] The method and basis set reasonably reproduced crystallographic data of manganese(I) carbonyl complexes such as $MnCl(CO)_5$[22] and (η^2-2-acetylphenyl)tetracarbonylmanganese,[23] while MP2 calculations using the same basis set gave much shorter Mn−CO bond lengths than the experimental data (differences more than 5%), probably because of the overestimation of back-donation (see Supporting Information).[24] Each stationary point was adequately characterized by normal coordinate analysis. For all of the pathways reported in the text, intrinsic reaction coordinate (IRC) analysis[25] was carried out to confirm that the stationary points are smoothly connected to each other. Natural population analysis (NPA) was performed on the

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(17) For instance, a manganese complex bearing one acac ligand, one acetylene ligand, and three CO ligands goes through essentially the same reaction pathway as the present model complex except for the involvement of a CO dissociation step, which causes significant destabilization (see Scheme S1).
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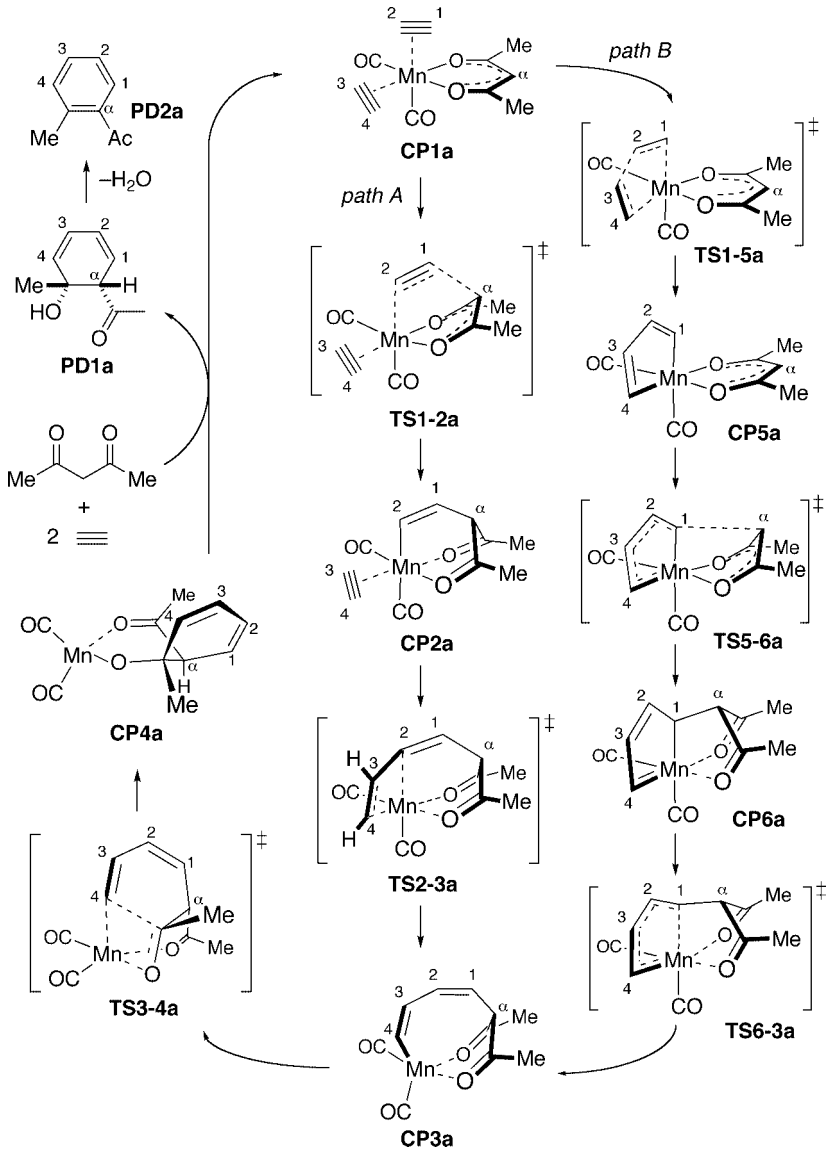
Scheme 8. Reaction Pathways of [2 + 2 + 2] Annulation of Acetyleacetone and Acetylene on Manganese



stationary points at the same level of theory.[26] The Boys localization procedure was performed to obtain localized Kohn−Sham orbitals.[27]

To confirm the reliability of the relatively small basis set, single-point energy calculations were performed on the stationary points at the B3LYP/631LAN level using larger basis sets; that is, the SDD basis set consisting of the Stuttgart/Dresden ECP for Mn[28] and 6-311+G(d,p) for the rest (denoted as 6311SDD). The same basis sets were used to obtain single-point energies by the self-consistent reaction field (SCRF) method based on the polarized continuum model (CPCM, $\varepsilon =$ 2.379 for toluene).[29] These SCRF single-point energies will be used to describe the reaction energetics throughout this article. The effects of the solvent polarity on the energy profiles were found to be generally small (1−2 kcal/mol). Note also that the free energy correction to the potential energy profile (obtained at the B3LYP/631LAN level) exerted moderate effects (several kcal/mol), probably because all the reaction steps are intramolecular (i.e., small entropy effects).

Scheme 8 and Figure 2 show a summary of the reaction pathways and the energetics of the Mn-catalyzed [2 + 2 + 2] annulation reaction proposed in this article. We identified two reaction pathways (paths A and B) that smoothly connect the initial complex **CP1a** and a manganese alkoxide complex **CP4a**, which can liberate at the end of the catalytic cycle a cyclohexadienol product **PD1a** and regenerate **CP1a** through ligand exchange and deprotonation with one molecule of acetylacetone and two molecules of acetylene. Path A involves carbometalation of the manganese enolate to acetylene (**CP1a** to **CP2a**),

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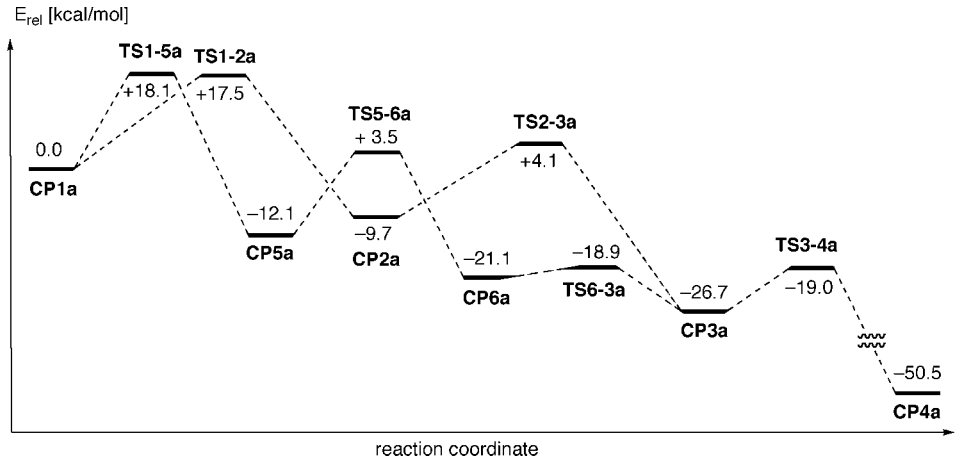

Figure 2. Energy diagram (in kcal/mol) of the [2 + 2 + 2] annulation reaction obtained at the B3LYP/6311SDD (CPCM, $\varepsilon = 2.379$ for toluene)//631LAN level.

acetylene insertion into the Mn−C bond (**CP2a** to **CP3a**), and intramolecular addition of the dienylmanganese complex to the carbonyl group (**CP3a** to **CP4a**).

In path B, two acetylene ligands undergo oxidative cyclization first (**CP1a** to **CP5a**). The enolate moiety of the manganacyclopentadiene intermediate **CP5a** attacks the C1 atom to give another manganacycle **CP6a**. Cleavage of the Mn−C1 bond of **CP6a** results in the formation of **CP3a**, which is a common intermediate in path A and B, and leads to the product complex **CP4a**. Details of each reaction pathway will be discussed below.

Path A: Enolate Carbometalation Route. a. Addition of Manganese Enolate to Acetylene. Figure 3 shows the structures of the stationary points along path A−[2 + 2 + 2] annulation through carbometalation of manganese enolate. In the initial complex **CP1a**, one acetylene ligand cis to the acac ligand is weakly bound to the Mn center (Mn−C1 = 2.87 Å, Mn−C2 = 2.96 Å), while the other ligand on the acac plane is strongly coordinating (Mn−C3 = 2.28 Å, Mn−C4 = 2.17 Å). The weaker coordination of the former acetylene ligand is due to the strong trans influence of the CO ligand. The C1 and Cα atoms are too far away from each other (3.58 Å) to have any interaction. **CP1a** undergoes carbometalation through a concerted cyclic transition state (TS, **TS1-2a**) with an activation energy of 17.5 kcal/mol. Formation of the resulting vinylmanganese intermediate **CP2a** is moderately exothermic (ΔE = −9.7 kcal/mol). Note that the orientation of the second acetylene changes after the carbometalation, i.e., it becomes perpendicular to the acac plane in **CP2a**.

The forming C2−Mn and C1−Cα bonds in **TS1-2a** have almost the same length (2.32 and 2.31 Å, respectively). Judging from the C2−Mn and C1−Cα bond lengths in the intermediate **CP2a** (2.04 and 1.54 Å, respectively), the formation of the C2−Mn bond is apparently much more advanced than that of the C1−Cα bond. Different degrees of rehybridization of the C1 and C2 atoms, as indicated by the bond angles (H−C1−C2 = 162°, C1−C2−H = 135°), also demonstrate the advanced nature of the C2−Mn bond formation. The NPA indicates considerable polarization of the C1≡C2 triple bond during the carbometalation. Thus, the negative charge on C1 decreases upon going from **CP1a** to **TS1-2a** (−0.24 to −0.14), whereas that on C2 significantly increases (−0.24 to −0.43).

These structural and electronic features of the Mn enolate addition are typical of carbometalation reactions[30] and suggest that the regioselectivity of this step is controlled by electronic effects (vide infra). The geometries and energetics of the Mn enolate reaction closely resemble the In enolate reaction that we reported recently (Figure 4).[10b] Thus, the lengths of the forming C−C and metal−C bonds differ by less than 0.1 Å, and the bending angles of acetylene by only 1° (Figure 4a). The activation energies and reaction energies are also very similar, the differences being less than 1 kcal/mol (Figure 4b). We suspect that the rhenium-catalyzed reaction of a 1,3-dicarbonyl compound with an alkyne also takes place through a similar enolate carbometalation mechanism.[11]

b. Insertion of Acetylene into the Vinyl-Manganese Bond. In the vinylmanganese intermediate **CP2a**, the remaining acetylene ligand is parallel to the Mn−vinyl bond and hence is ready for insertion into the Mn−C bond. The insertion takes place through a four-centered TS (**TS2-3a**) with an activation energy of 13.8 kcal/mol. Formation of a dienylmanganese intermediate **CP3a** from **CP2a** is exothermic by 17.0 kcal/mol. **TS2-3a** can be regarded as a much tighter TS than the enolate carbometalation TS (**TS1-2a**), as judged from the lengths of the forming C4−Mn and C2−C3 bonds (1.99 and 1.91 Å, respectively). Considerable rehybridization of the C3 and C4 atoms (i.e., the H−C3−C4 and C3−C4−H angles are 141° and 138°, respectively) also supports this conjecture. These characteristics suggest that the acetylene insertion is susceptible to steric effects (vide infra). In contrast to the initial carbometalation step, the C3≡C4 triple bond in the insertion step is little polarized, as indicated from NPA charges on the C3 (−0.25) and C4 (−0.27) atoms in **TS2-3a**. While the complexes **CP1a** and **CP2a** take octahedral structures, the coordination geometry of **CP3a** is a distorted square pyramidal, where one of the CO ligands occupies the apical position and the other ligands are on the equatorial plane.

Analysis of localized Kohn−Sham orbitals of the alkyne insertion TS (**TS2-3a**) demonstrated typical orbital interactions for insertion reactions of olefins/alkynes into transition metal−carbon bonds (Figure 5).[24,31] Figure 5a illustrates the

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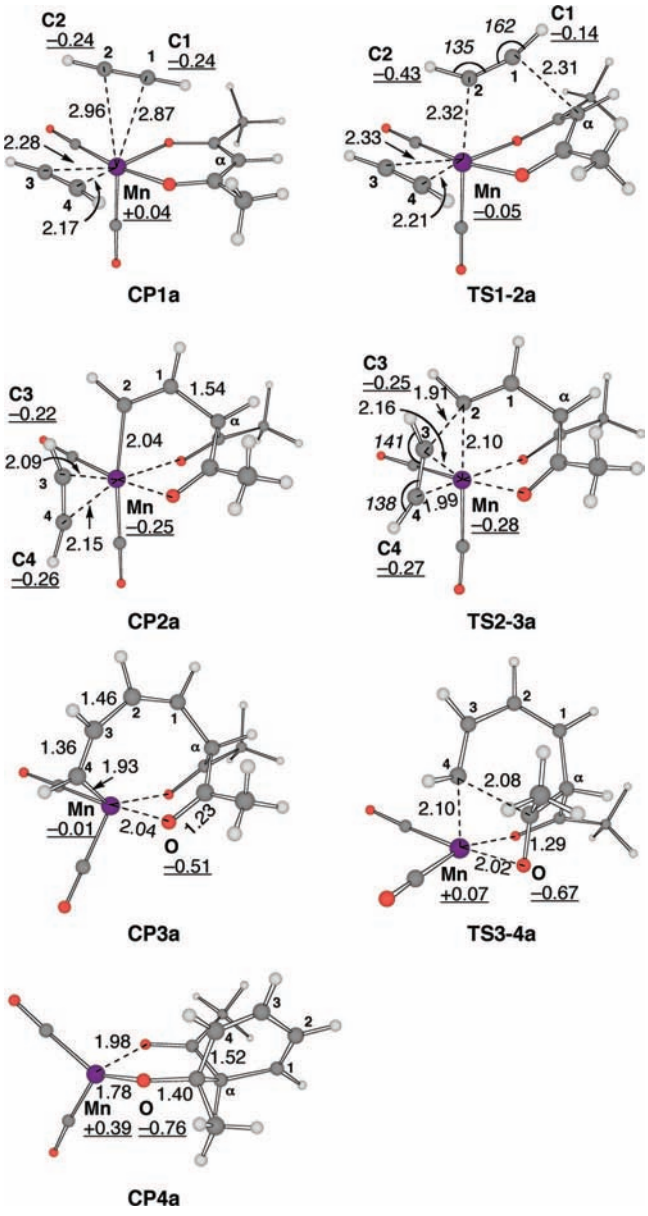

Figure 3. Structures of stationary points on the enolate carbometalation pathway. Carbon, gray; hydrogen, white; oxygen, red; manganese, purple. Bond lengths (Å), bond angles (deg), and NPA charges are in plain, in italic, and underlined, respectively.

bonding interaction between Mn−C2 σ and C3≡C4 π* orbitals. The localized orbital shown in Figure 5b basically consists of Mn−C2 σ* and C3≡C4 π orbitals, while there is involvement of a significant contribution of a 2p orbital of the vinylic C2 carbon, which points toward the acetylene and thus effectively interacts with the C3≡C4 π orbital. These Mn−C σ orbital/C≡C π orbital interactions should serve as an essential driving force for the alkyne insertion. We can expect that a similar mechanism operates also in the Re-catalyzed [2 + 2 + 2] annulation reaction (eq 3) and that the unavailability of a high-lying d orbital is a possible reason why indium never catalyzes such a reaction.

c. Intramolecular Carbonyl Addition of the Dienylmanganese Complex. In the 16-electron dienylmanganese complex **CP3a**, the final ring closure step takes place readily by addition of the dienylmanganese moiety to the carbonyl group ($\Delta E^{\ddagger}$ = 7.7 kcal/mol) through **TS3-4a** to form **CP4a**. The formation of

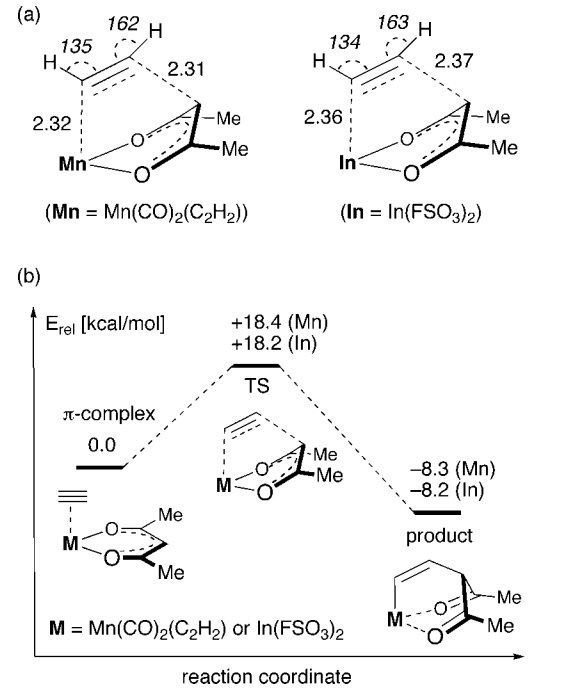

Figure 4. Comparison of addition of Mn and In enolates to acetylene. (a) Geometries of transition states. Bond lengths (Å) and bond angles (deg) are shown in plain and in italic, respectively. (b) Energy diagrams (gas phase, kcal/mol). Values for the In enolate are taken from ref 10b.

the alkoxide complex **CP4a** (although it is a 14-electron complex) is exothermic by 23.8 kcal/mol. Features of this step include (1) sp^2-to-sp^3 hybridization of the carbonyl group (sum of bond angles around the carbonyl carbon is 345° in **TS3-4a**), (2) elongation of the C═O bond, and (3) accumulation of negative charge on the carbonyl oxygen atom (−0.51, −0.67, and −0.76 in **CP3a**, **TS3a-4a**, and **CP4a,** respectively) and

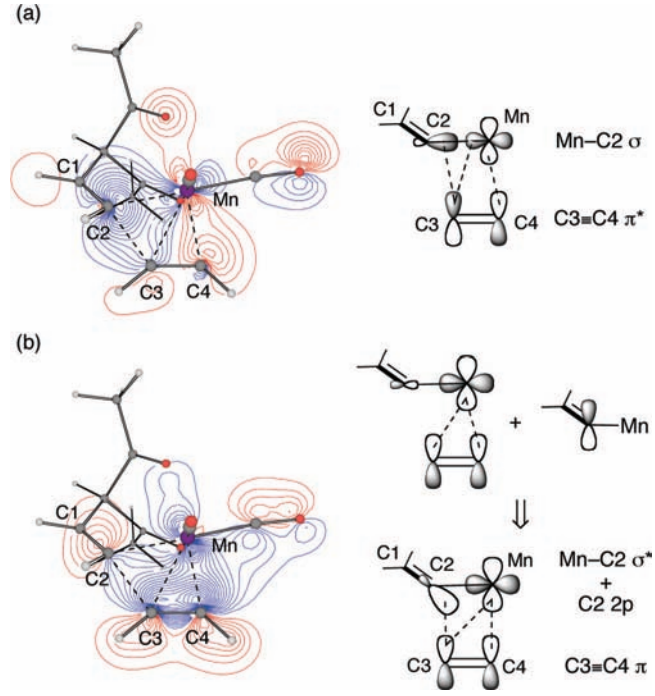

Figure 5. Orbital interactions in the alkyne insertion TS. Localized Kohn−Sham orbitals of **TS2-3a** (left, contour intervals are 0.015 e·au^{-3}) and their schematic representations (right).

positive charge on the Mn atom (−0.01, +0.07, and +0.39), all of which are typical of nucleophilic carbonyl additions of organometallics.[32] The coordination geometry around the Mn center is square pyramidal in **TS3-4a** (the C4 atom occupies the apical position), which finally becomes distorted tetrahedral in the product complex **CP4a**. In agreement with the experiment (eq 4 and Figure 1), the alkoxide and acetyl groups on the cyclohexadiene ring of **CP4a** are cis to each other.

d. Catalyst Turnover and Overall Energetics. The manganese alkoxide complex **CP4a** can undergo ligand exchange (involving proton transfer) with one molecule of acetylacetone and two molecules of acetylene to liberate a cyclohexadienol product (**PD1a**) and regenerate the initial complex **CP1a** (Scheme 8). The energy change calculated for this process is −23.2 kcal/mol, indicating that the catalyst turnover should be easy. The exothermicity for the conversion of one acetylacetone molecule and two acetylene molecules into the cyclohexadienol was calculated to be 73.6 kcal/mol. This large exothermicity is mainly due to the release of C≡C triple bond strains, the formation of three new C−C single bonds, and the conjugation of the diene moiety. The absence of any high energy barrier or deep energy well along the reaction pathway (Figure 2) suggests that the enolate carbometalation mechanism (path A) is a viable mechanism for the [2 + 2 + 2] annulation. The rate-limiting step in this mechanism is likely to be the initial enolate carbometalation.

Path B: Oxidative Cyclization Route. Figure 6 shows the structures of the stationary points that connect the initial complex **CP1a** and dienylmanganese intermediate **CP3a** through path B—the formation of a manganacyclopentadiene from two acetylene ligands. This process takes place through **TS1-5a** with an activation energy of 18.1 kcal/mol, which is close to that for the first step of path A (17.5 kcal/mol). The Mn atom and two acetylene ligands are in the same plane in **TS1-5a**, where the lengths of the forming C1−Mn, C2−C3, and C4−Mn bonds are 2.05, 2.05, and 2.04 Å, respectively. The degree of rehybridization of the C3≡C4 acetylene is slightly more advanced than that of the C1≡C2 acetylene, judging from their bond angles. NPA charges on the C1−C4 atoms indicate little polarization of the acetylene ligands during the oxidative cyclization. The formation of the manganacyclopentadiene intermediate **CP5a** is exothermic by 12.1 kcal/mol, which is larger than the case of the enolate carbometalation (9.7 kcal/mol). The five-membered ring moiety of **CP5a** is slightly asymmetric, i.e., the C1−Mn bond (1.98 Å) is longer than the C4−Mn bond (1.89 Å), probably because of the strong trans influence of the CO ligand.

The enolate moiety of **CP5a** then undergoes nucleophilic attack on the C1 atom of the manganacyclopentadiene moiety through **TS5-6a** ($\Delta E^{\ddagger}$ = 15.6 kcal/mol). This causes bond alternation of the manganacycle and leads to a *manganacyclopenta-1,3-diene* intermediate **CP6a**. The formation of **CP6a** is slightly exothermic (ΔE = −9.0 kcal/mol). Several examples

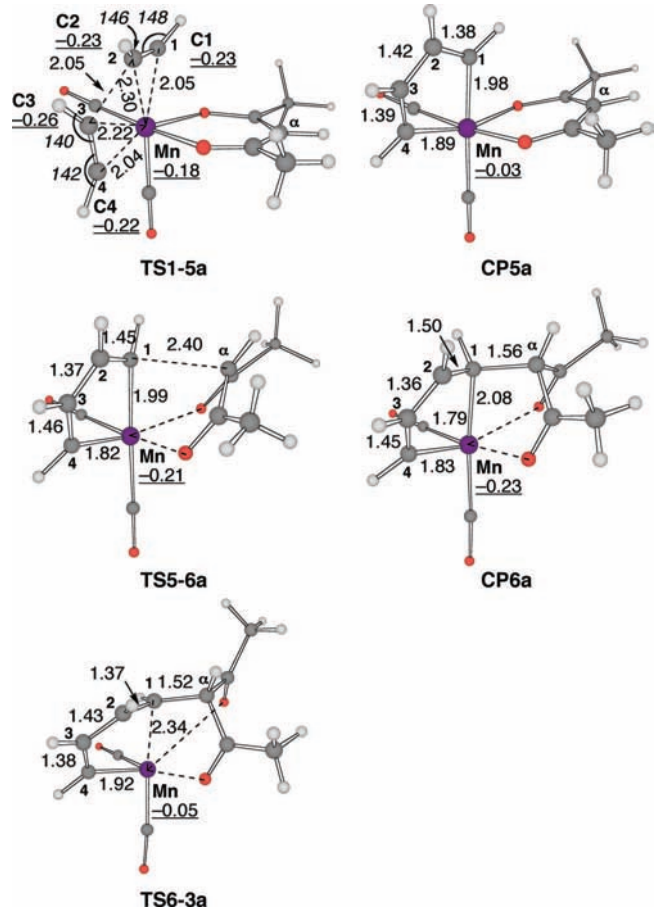

Figure 6. Structures of the stationary points on the oxidative cyclization pathway. Carbon, gray; hydrogen, white; oxygen, red; manganese, purple. Bond lengths (Å), bond angles (deg), and natural charges are in plain, in italic, and underlined, respectively.

of metallacyclopenta-1,3-diene complexes have been reported,[33] and one of them has been synthesized by intramolecular attack of an anionic carbon ligand on a metallacyclopenta-2,4-diene moiety (i.e., the same manner as the conversion of **CP5a** to **CP6a**).[33d] The C4−Mn bond length of 1.83 Å is comparable to previously reported manganese(I) carbene complexes.[34] The complex **CP6a** rearranges into the dienylmanganese complex **CP3a** by cleavage of the C1−Mn bond (**TS6-3a**). This step requires an activation barrier as low as 2.2 kcal/mol and is only slightly exothermic (ΔE = −5.6 kcal/mol). A related rearrangement reaction has been reported for an iridacycle complex.[33a] The complex **CP3a** eventually leads to the annulation product as already discussed above. The overall energy profile (Figure 2) suggests that path B is also a viable route for the [2 + 2 + 2] annulation reaction. The rate-limiting step for this pathway is the formation of the manganacyclopentadiene.

Regioselectivity of [2 + 2 + 2] Annulation. The above model studies using unsubstituted acetylene indicated that both the enolate carbometalation (path A) and the manganacyclopentadiene routes (path B) are equally feasible. However, the studies described in this section indicate that path A not only becomes

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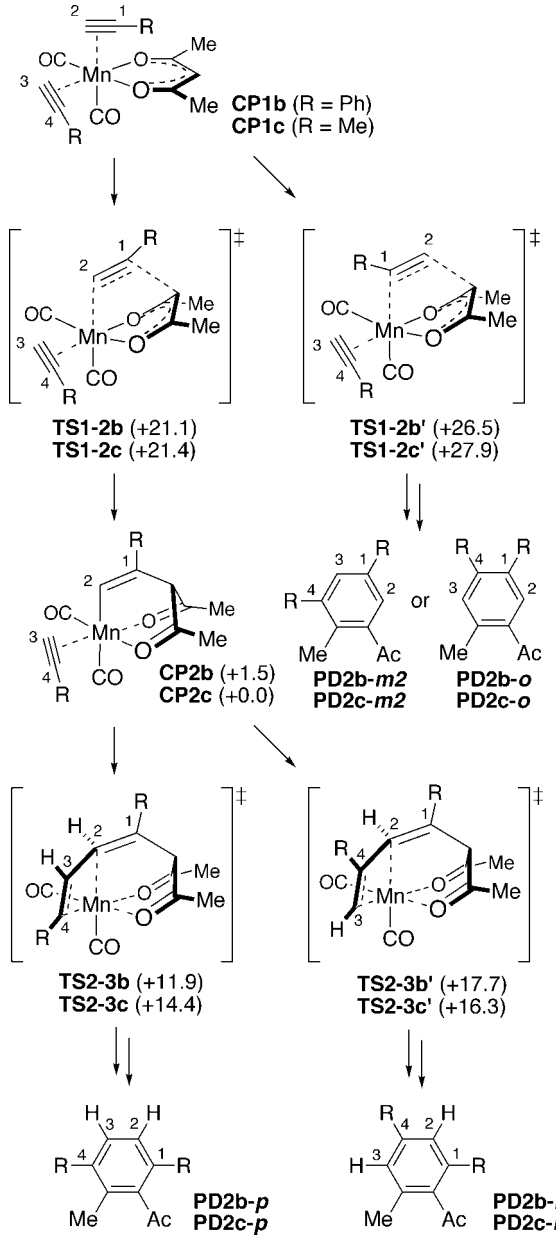
Scheme 9. Regioisomeric Reaction Pathways of Phenylacetylene and Propyne Complexes through Enolate Carbometalation/ Acetylene Insertion[a]



[a] Values in parentheses refer to energies (B3LYP/6311SDD (CPCM, ε = 2.379 for toluene)//631LAN, kcal/mol) relative to the initial complex.

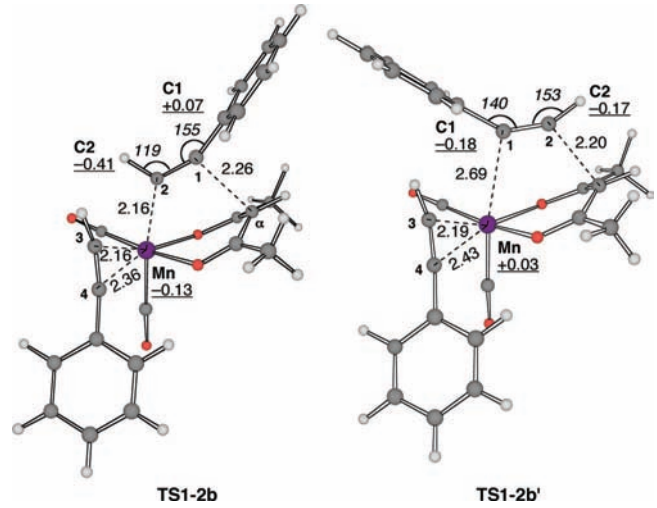


Figure 7. TS structures of enolate carbometalation with phenylacetylene. Carbon, gray; hydrogen, white; oxygen, red; manganese, purple. Bond lengths (Å), bond angles (deg), and natural charges are in plain, in italic, and underlined, respectively.

energetically favored when phenylacetylene or propyne are used as the substrate but also reproduces the experimental regioselectivity. Path A puts together two alkynes through two consecutive carbometalation reactions, which were found to differ in their character, to exhibit different regioselectivity, and hence to result in the experimentally observed regioselectivity (Scheme 1).

a. Regioselectivity of Path A, Enolate Carbometalation Route. In path A, the regiochemistry of the final product is governed by the regioselectivity of both the enolate addition and the alkyne insertion steps (Scheme 9). In the first step, the manganese enolate may undergo C−C bond formation at either the internal (C1) or terminal (C2) carbon atom. The addition to the internal carbon atom requires activation energies of 21.1 kcal/mol for phenylacetylene (**TS1-2b**) and 21.4 kcal/mol for propyne (**TS1-2c**), while the addition to the terminal carbon was much less favored by 5−6 kcal/mol for both cases (**TS1-2b′** and **TS1-2c′**). This energy difference predicts that the first step takes place with >99.9:0.1 selectivity at 65 °C and is entirely consistent with the experimental lack of the isomers **PD2b-*m*2**/**PD2b-*o*** and **PD2c-*m*2**/**PD2c-*o***.

The calculated regioselectivity for this step is typical of carbometalation reactions (Figure 7).[9,10,30] The phenylacetylene in **TS1-2b** is suitably polarized (C1 = +0.07, C2 = −0.41) for tight interaction with the Mn enolate (C2−Mn = 2.16 Å, C1−Cα = 2.26 Å), while the populations of the C1≡C2 bond in **TS1-2b′** (C1: −0.18, C2: −0.17) causes the C1 atom to interact poorly with the Mn atom (C1−Mn = 2.69 Å). We found the same trends of structures and populations for the propyne reaction.

The second step is the alkyne insertion into the Mn−vinyl bond taking place from the first intermediates **CP2b** and **CP2c**. In this step, a new C−C bond can form between the C2 and C3 atoms (**TS2-3b**, **TS2-3c**) or the C2 and C4 atoms (**TS2-3b′**, **TS2-3c′**), which finally leads to a para-substituted product (**PD2b-*p***, **PD2c-*p***) or a meta-substituted product (**PD2b-*m*1**, **PD2c-*m*1**), respectively. For the case of phenylacetylene, **TS2-3b** is much preferred to **TS2-3b′** by 5.8 kcal/mol, which again corresponds to a virtually perfect regioselectivity (>99.9:0.1). In contrast, the energy difference of the two insertion TSs is much smaller for propyne (**TS2-3c** vs **TS2-3c′**, 1.9 kcal/mol). The TS energy difference of 1.9 kcal/mol corresponds to a kinetic ratio of ca. 94:6 at 65 °C. Overall, the calculated energy profiles agree qualitatively with the experimental observations (i.e., exclusively para-selective for aryl acetylenes and para/meta ratio of ca. 3:1 for alkyl acetylenes).

In contrast to the enolate carbometalation step (Figure 7), the geometries of the manganese coordination spheres of the two regioisomeric, four-centered insertion TSs greatly resemble each other (Figure 8). The forming and breaking C−Mn and C−C bond lengths in **TS2-3b** and **TS2-3b′** differ from each other by less than 0.1 Å. The structures and NPA charges of the phenylacetylene moieties are also almost the same. This trend also holds for the reaction of propyne. Thus, we surmise that the regioselectivity of the alkyne insertion step is mainly

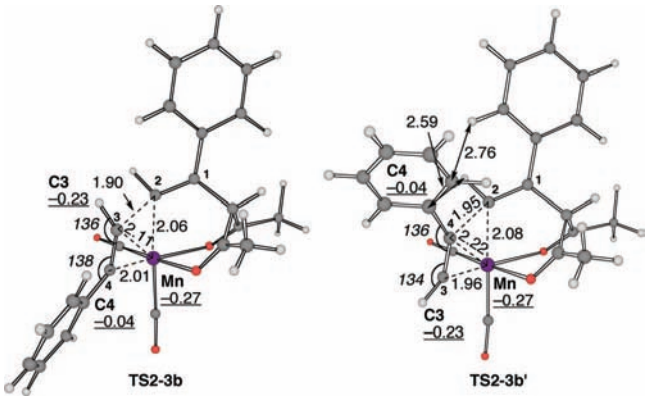
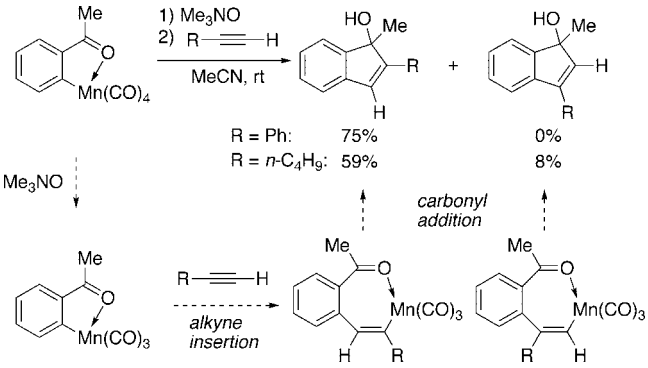


Figure 8. TS structures of phenylacetylene insertion. Carbon, gray; hydrogen, white; oxygen, red; manganese, purple. Bond lengths (Å), bond angles (degrees), and natural charges are in plain, in italic, and underlined, respectively.

Scheme 10. Indene Formation from ortho-Manganated Aryl Ketone and Alkyne (ref 15a)

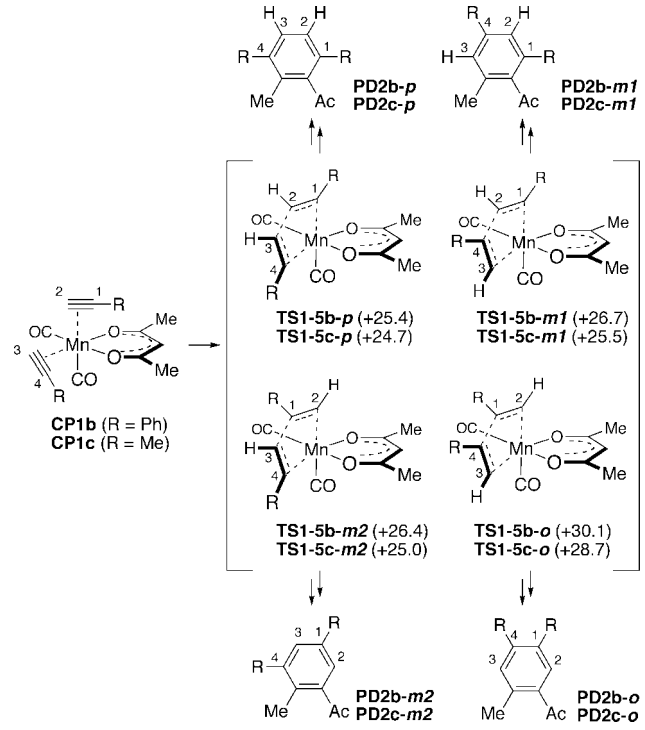


controlled by steric rather than electronic effects (i.e., repulsion between the phenyl group of $HC^3{\equiv}C^4Ph$ and the alkenyl group).[35]

Finally, we point out the kinship of the second carbometalation step to the aryl−vinyl bond formation step in the stoichiometric indene formation reaction between an isolated ortho-manganated aryl ketone and an alkyne (Scheme 10),[15] which exhibits regioselectivity very similar to the second carbometalation. On the basis of the present calculations, we can consider that the indene formation reaction involves removal of a CO ligand by Me_3NO, alkyne insertion into the aryl−Mn bond, and addition of the alkenyl manganese to the carbonyl group. The first C−C bond formation step of this reaction is probably similar to the second carbometalation step in light of the coordination environment of the Mn atom (cf. Scheme 9, **TS2-3b(c)** vs **TS2-3b(c′)**).

b. Regioselectivity of Path B, Manganacyclopentadiene Route. The regioselectivity of the formation of the manganacyclopentadiene is important in path B, and we studied the reaction of the phenylacetylene (**CP1b**) and propyne complexes (**CP1c**) (Scheme 11). There exist a priori four regioisomeric TSs, three of which are found to be equally energetically favored (energy difference less than 1 kcal/mol); that is, **TS1-5b-*p*/TS1-5b-*m*1/TS1-5b-*m*2** or **TS1-5c-*p*/TS1-5c-*m*1/TS1-5c-*m*2** lead

Scheme 11. Regioisomeric Reaction Pathways of Phenylacetylene and Propyne Complexes through Oxidative Cyclization[a]



[a] Values in parentheses refer to energies (B3LYP/6311SDD (CPCM, ε = 2.379 for toluene)//631LAN, kcal/mol) relative to the initial complex.

respectively to para (**PD2b-*p*** or **PD2c-*p***) or meta products (**PD2b-*m*1/PD2b-*m*2** or **PD2c-*m*1/PD2c-*m*2**). The remaining TS (**TS2b-*o*** or **TS2c-*o***), which gives an ortho-substituted benzene product (**PD2b-*o*** or **PD2c-*o***), is disfavored by as much as ca. 4 kcal/mol because of the steric repulsion of the two R groups. The energetics predicts the formation of a mixture of three regioisomers for both the phenylacetylene and propyne cases (product ratios (***p*/*m*1/*m*2/*o***) calculated to be 74:10:16:< 0.1 and 49:16:34:0.1, respectively, at 65 °C), which does not agree with the experimental observation.

Unlike the equal viability of the two paths for the unsubstituted acetylene (vide supra), path B in the phenylacetylene and the propyne models needs much higher activation energies (25−27 kcal/mol) than path A (ca. 21 kcal/mol, Scheme 9). The energy differences indicate that the contribution of path A is dominant (99.7% for phenylacetylene and 98.5% for propyne). Therefore, on the basis of the difference of the activation barriers for paths A and B, as well as the regioselectivity expected for each path, we conclude that path A is the favored path of the manganese-catalyzed [2 + 2 + 2] annulation reaction.

In summary, we conclude that the Mn-catalyzed [2 + 2 + 2] annulation reaction of a 1,3-dicarbonyl compound and an alkyne takes place predominantly through path A, which involves consecutive carbometalation of two alkynes. The theoretical studies indicated first that path A is greatly favored over path B when the alkyne is phenylacetylene or propyne and that path B may occur competitively when it is acetylene. The formation of the 1:1 diketone/acetylene adduct **7** (Scheme 4) is a direct experimental support for the first conclusion, i.e., the presence of the putative first intermediate **CP2b** in path A, and the formation of acetylene trimerization side product **9**, which is probably formed via a manganacyclopentadiene intermediate (Scheme 5), may support the operation of path B.

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Thus, the experimentally observed reaction takes place through (1) addition of a manganese enolate of a 1,3-dicarbonyl compound to a terminal alkyne to give a vinylmanganese complex where the metal is attached to the terminus of the alkyne, (2) insertion of a second alkyne into the vinyl−Mn bond to give a dienylmanganese complex where the metal becomes attached to the substituted side of the alkyne, and (3) intramolecular nucleophilic addition of the dienylmanganese to the carbonyl group (Scheme 3). The transition metal nature of the manganese metal is essential in the second carbometalation, while it is not in the first carbometalation. This three-step mechanism accounts for the experimental results including (1) the cis stereochemistry of the cyclohexadienol product (eq 4), (2) the high para regioselectivity in the reaction of aryl acetylenes (Scheme 1a), and (3) the moderate regioselectivity for alkyl acetylenes (Scheme 1b). The mechanism is also consistent with the absence of reactivity of cyclic 1,3-diketones. An alternative path, path B, fails to explain the characteristic regioselectivity of the reaction. The diversity of the reactivity of organomanganese(I) complexes demonstrated in the [2 + 2 + 2] annulation reaction will offer valuable implications for the further development of synthetic transformations catalyzed by Group 7 transition metal complexes, which have so far attracted much less attention than their early and late neighbors.

Experimental Section

General. All reactions dealing with air- or moisture-sensitive compounds were carried out in a dry reaction vessel under a positive pressure of argon or nitrogen. Air- and moisture-sensitive liquids or solutions were transferred via a syringe or Teflon cannula. Analytical thin-layer chromatography was performed on a glass plate precoated with 0.25-mm 230−400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light (UV) and/or by immersion in an acidic solution of *p*-anisaldehyde or PMA followed by heating on a hot plate. Flash column chromatography was performed as described by Still et al.,[36] employing Kanto Silica Gel 60 (spherical, neutral, 140−325 mesh).

Materials. Commercial reagents were purchased from Tokyo Kasei Co., Aldrich Inc., and other commercial suppliers and were either distilled or recrystallized before use. Toluene was distilled over CaH_2. The water content of the solvent was determined on a Karl Fischer moisture titrator to be less than 20 ppm. Anhydrous ethereal solvents (stabilizer free) were purchased from Wako Pure Chemical Industries and purified by a solvent purification system (GlassContour).[37]

Instrumentation. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were measured on a JEOL ECA-500 or ECX-400 spectrometer and reported in ppm from tetramethylsilane. ^{1}H NMR spectra in $CDCl_3$ were referenced internally to tetramethylsilane as a standard, and ^{13}C spectra to the solvent resonance ($CDCl_3$, 77.0 ppm). APCI mass spectra were taken on a JEOL Accu JMS-T100LC. EI mass spectra were taken on a Shimadzu Parvum 2 gas chromatograph mass spectrometer.

(36) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(37) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H. *Organometallics* **1996**, *15*, 1518–1520.

(1*S,6*R**)-Ethyl-6-fluoro-6-hydroxy-1-methyl-2,5-diphenylcyclohexa-2,4-dienecarboxylate (4).** Ethyl 2-fluoro-3-oxobutanoate (74 mg, 0.50 mmol), phenylacetylene (157 mg, 1.50 mmol), and $MnBr(CO)_5$ (13.7 mg, 0.05 mmol) were added to a dried Schlenk tube. After stirring at 80 °C for 5 h, the mixture was cooled to room temperature. The resulting mixture was filtered through a pad of silica gel using ether as an eluent. The filtrate was concentrated in vacuo to obtain the crude product. Flash-column chromatography (silica gel, hexane/ethyl acetate = 90:10 to 80:20 to 70:30) gave the title compound (17 mg, 0.05 mmol, 10%) as a pale yellow solid. Crystals suitable for X-ray diffraction analysis were obtained by recrystallization from hexane. Pale yellow solid; mp 107−108 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (t, J = 7.2 Hz, 3H), 1.71 (d, J = 3.5 Hz, 3H), 4.21−4.34 (m, 2H), 6.05 (d, J = 5.9 Hz, 1H), 6.41 (dd, J = 2.3, 5.9 Hz, 1H), 7.29−7.39 (m, 6H), 7.46 (d, J = 6.9 Hz, 2H), 7.51 (dd, J = 1.7, 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 22.3 (d, $^3J_{C-F}$ = 11.9 Hz), 62.0, 78.6 (d, $^2J_{C-F}$ = 22.7 Hz), 100.7 (d, $^1J_{C-F}$ = 191.7 Hz), 121.3 (d, $^3J_{C-F}$ = 2.7 Hz), 125.8 (d, $^3J_{C-F}$ = 5.7 Hz), 126.78 (2C), 126.80 (2C), 128.0, 128.03, 128.07 (2C), 128.4 (2C), 136.1, 136.4 (d, $^2J_{C-F}$ = 23.3 Hz), 137.0, 145.5 (d, $^3J_{C-F}$ = 5.1 Hz), 168.6 (d, $^2J_{C-F}$ = 30.4 Hz). MS(APCI+) 352 (M^+).

Ethyl-2-phenyl-3,6-di(2-methoxyphenyl)benzoate (8) and 1,2,4-(2-Methoxyphenyl)Benzene (9). $MgSO_4$ (12.0 mg, 0.10 mmol) was dried in a Schlenk tube using a flame. Ethyl benzoylacetate (95 mg, 0.50 mmol), 2-ethynyl anisole (198 mg, 1.5 mmol), and 0.5 mL of toluene were added to the dried $MgSO_4$, followed by $MnBr(CO)_5$ (14 mg, 0.050 mmol) and NMO (5.9 mg, 0.050 mmol). After stirring at 65 °C for 144 h, the reaction mixture was cooled to room temperature, diluted with ether and filtered through a pad of silica gel using ether as an eluent. The filtrate was concentrated in vacuo to obtain the crude product. Flash-column chromatography (silica gel, hexane/ether = 90:10 to 80:20 to 60:40) gave the title compounds (**8**, 173 mg, 0.39 mmol; **9**, 53 mg, 0.13 mmol). Physical properties of compound **8** were in accordance with those reported in the literature.[6] Compound **9**: R_f = 0.36 (hexane/ethyl acetate = 80:20); White solid; mp 99−101 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.47 (s, 3H), 3.49 (s, 3H), 3.84 (s, 3H), 6.72 (t, J = 8.0 Hz, 2H), 6.82 (t, J = 7.5 Hz, 3H), 6.99 (d, J = 8.0 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 7.12−7.16 (m, 4H), 7.29−7.33 (m, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 54.89, 54.91, 55.5, 110.17, 110.18, 111.1, 119.8, 120.7, 127.9, 128.2, 128.4, 130.4, 131.1, 131.49, 131.54, 137.0, 156.26, 156.27, 156.6 (several peaks are overlapped.); MS(EI) *m*/*z* 396 (M^+).

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Supporting Information Available: Additional computational results, energies and Cartesian coordinates of stationary points, full citations of the Gaussian program, and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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