Pauson–Khand Reaction

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Well-Defined Models for the Elusive Dinuclear Intermediates of the Pauson–Khand Reaction

*Douglas R. Hartline, Matthias Zeller, and Christopher Uyeda**

***Abstract:** The mechanism of the Pauson–Khand reaction has attracted significant interest due to the unusual dinuclear nature of the $Co_2(CO)_x$ active site. Experimental and computational data have indicated that the intermediates following the initial $Co_2(CO)_6$(alkyne) complex are thermodynamically unstable and do not build up in appreciable concentrations during the course of the reaction. As a consequence, the key steps that control the scope of viable substrates and various aspects of selectivity have remained largely uncharacterized. Herein, a direct experimental investigation of the dinuclear metallacycle-forming step of the Pauson–Khand reaction is reported. These studies capitalize on well-defined d^9–d^9 dinickel complexes supported by a naphthyridine–diimine (NDI) pincer ligand as functional surrogates of $Co_2(CO)_8$.*

Cycloaddition reactions are key targets for the development of new synthetic methods, providing efficient routes to ring systems from comparatively simple linear precursors. Transition-metal-mediated processes have significantly expanded the scope of viable cycloadditions beyond the subset that are favorable under thermal conditions.[1] The Pauson–Khand reaction is one of the earliest examples and represents a prototype for three-component couplings.[2,3] The reaction produces cyclopentenones from the selective union of an alkene, an alkyne, and CO. Despite its 40-year history, and numerous applications in organic synthesis,[4] little is known about the mechanism of the Pauson–Khand reaction. The initial ligand substitution step between $Co_2(CO)_8$ and the alkyne component is well-characterized—over 500 crystal structures of $Co_2(CO)_6$(alkyne) adducts have been reported[5]—however, no subsequent intermediates are detectable under standard reaction conditions. Given the unique role that metal–metal bonds are thought to play in the Pauson–Khand reaction, a detailed understanding of the elementary steps would aid in the development of multinuclear platforms for a broader range of cycloadditions.

The energetic landscape of the Pauson–Khand reaction poses particular challenges for probing mechanism. The isolable $Co_2(CO)_6$(alkyne) complexes that initiate the reaction are themselves relatively inert but upon endothermic loss of CO engage the alkene in a series of rapid and irreversible steps leading to cyclopentenone formation.[6] In the absence of detectable intermediates, the working model advanced by Magnus and Principe based on stereochemical experiments has become commonly accepted.[7] The proposed mechanism comprises a sequence of oxidative coupling, CO insertion, and C–C reductive elimination steps, taking place across a Co–Co bond (Figure 1 a). Of particular interest is the alkene–alkyne coupling step, which is thought to be regio- and stereoselectivity determining. DFT models have suggested that the dinuclear nature of the active site might facilitate this coupling through a stabilizing Co–π interaction that is absent in analogous mononuclear pathways.[8] To date, no experimental systems have been identified that allow this hypothesis to be tested.

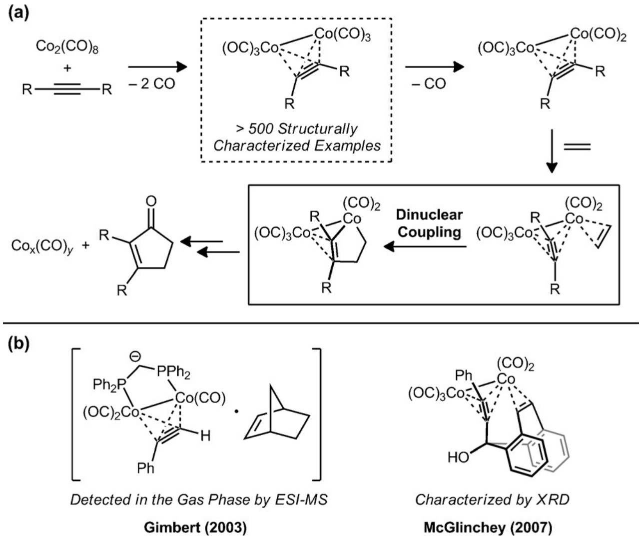

Figure 1. a) Proposed dinuclear mechanism for the Pauson–Khand reaction (Ref. [7]). b) Previous experimental characterization of the post-alkyne-complex intermediates.

Herein, we report the first direct characterization of a dinuclear alkene–alkyne coupling process relevant to the Pauson–Khand reaction and describe the structure of the associated metallacycle complex.[9] Our approach circumvents the long-standing challenge associated with studying $Co_2(CO)_8$ by utilizing a well-defined d^9–d^9 Ni_2 complex as a functional model.[10] These results complement experiments reported by the groups of Gimbert,[11] McGlinchey,[12] and Verdaguer,[13] which access unstable intermediates along the Pauson–Khand pathway by conducting reactions in the gas phase or by using unreactive, conformationally constrained enyne substrates (Figure 1 b).

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[*] D. R. Hartline, Dr. M. Zeller, Prof. C. Uyeda
Department of Chemistry
Purdue University
560 Oval Dr., West Lafayette, IN 47907 (USA)
E-mail: cuyeda@purdue.edu

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As an entry into Pauson–Khand reactivity, we first examined the accessibility of stable alkyne adducts using the [$^{i\text{-Pr}}$NDI]Ni_2 platform (NDI = naphthyridine–diimine).[10a] The [$^{i\text{-Pr}}$NDI]$Ni_2(C_6H_6)$ complex **1** undergoes ligand substitution with 1-phenyl-1-propyne (1.0 equiv), reaching full conversion into **2** within 1 h at room temperature. In the solid state (Figure 2 a), the bound alkyne ligand in **2** exhibits μ-η^2:η^2 coordination and is structurally analogous to previously reported $Co_2(CO)_6$(alkyne) complexes (Figure 2 b). Whereas the latter typically feature weak interactions between the two Co centers (an average Co–Co distance of 2.47 ± 0.02 Å among the examples in the Cambridge Structural Database),[14] the Ni–Ni distance in complex **2** is relatively short at 2.2751(6) Å, representing a significant contraction relative to the C_6H_6 complex **1** (Ni–Ni = 2.496(1) Å).

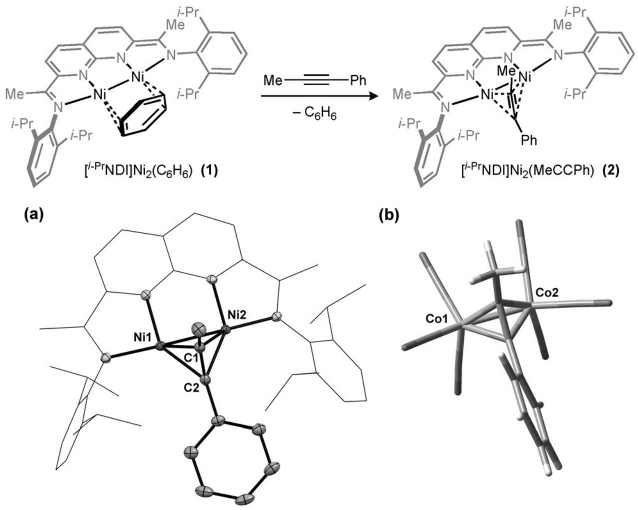
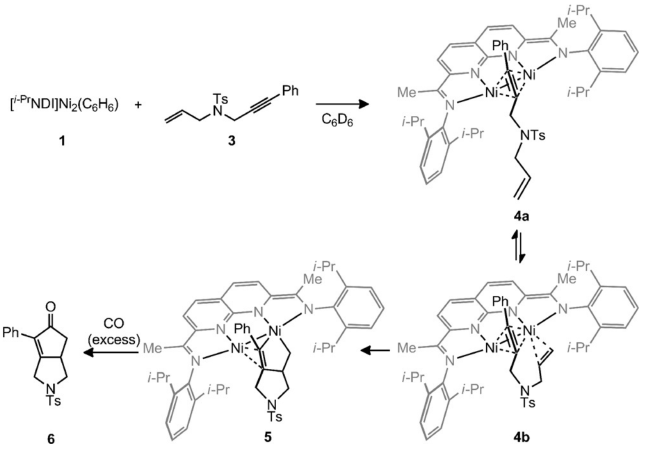


Figure 2. Top: Synthesis of the dinuclear μ-η^2:η^2-alkyne complex **2**. Bottom: a) Solid-state structure of **2** (thermal ellipsoids set at 50% probability) and b) computationally optimized structure of $Co_2(CO)_6$-(MeCCPh) (M06/6-31G(d,p); see the Supporting Information for details).

The enyne **3** was selected as a model substrate to probe alkene–alkyne coupling reactivity.[15] When complex **1** is combined with **3** (1.0 equiv) in C_6D_6, a transient adduct, **4**, is detected by ^{1}H NMR spectroscopy. Two possible structures of **4** are shown in Scheme 1, one in which only the alkyne is coordinated (**4a**) and the other involving coordination of both the alkyne and the alkene (**4b**). The two species are calculated to be close in energy with the latter being favored by 3.1 kcal mol^{-1}. The ^{1}H NMR spectrum of **4** exhibits apparent C_{2V} symmetry, consistent with a low-barrier pathway for the net rotation of the alkyne across the Ni–Ni bond. Additionally, significant contributions from an alkene-coordinated structure are evident in the upfield-shifted signals attributable to the two terminal protons of the alkene (doublets at $\delta = 4.16$ and 4.35 ppm). For the free substrate, these protons resonate at $\delta = 4.95$ and 5.14 ppm.

Upon standing at room temperature, the alkyne complex **4** converts to the C–C coupled product **5** (Scheme 1). The solid-state structure exhibits a notable correspondence to Magnus's proposed Pauson–Khand intermediate[7] and features a nickellacyclopentene fragment interacting in an η^2-fashion with the second Ni center (Figure 3). This Ni–π interaction induces significant rehybridization at the C1 and C2 positions toward the sp^3 limit, positioning the C2 substituent within the concave face of the bicyclic system (see Figure 3 a for atom labelling). Complex **5** is a competent intermediate en route to the terminal cyclopentenone product of the Pauson–Khand reaction. Exposure of **5** to an atmosphere of CO provides **6**, which was isolated in 78% yield over the two steps (Scheme 1).



Scheme 1. The Pauson–Khand reaction mediated by [NDI]Ni_2 complexes. Ts = *p*-toluenesulfonyl.

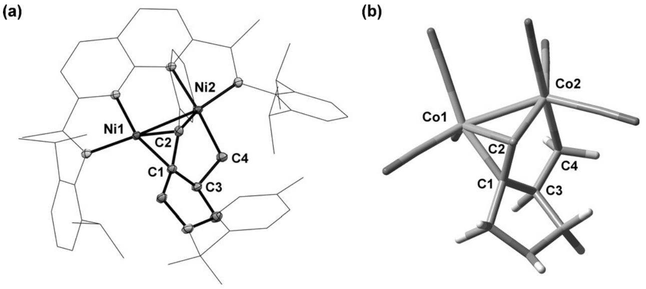


Figure 3. a) Solid-state structure of **5** (thermal ellipsoids set at 50% probability). b) Computationally optimized structure of the proposed metallacycle derived from $Co_2(CO)_8$ (M06/6-31G(d,p)).

The formation of complex **5** follows a first-order rate dependence on the concentration of the alkyne adduct **4**, consistent with the expected unimolecular mechanism for C–C coupling. The full reaction profile for the conversion of **1** and **3** into **5** is shown in Figure 4 a. The intermediate complex **4** is directly detectable by ^{1}H NMR spectroscopy and decays with a half-life of 53 min at 30 °C, corresponding to an activation free energy of 22.7 kcal mol^{-1}. To characterize the effect of electron-donating and withdrawing groups on the rate of metallacycle formation, we examined enyne derivatives bearing CF_3 (**3**-CF_3) and NMe_2 (**3**-NMe_2) substitution at the *para* position of the aryl ring (Figure 4 b). Transition-metal-mediated couplings between π components are generally described as being oxidative from the perspective of the

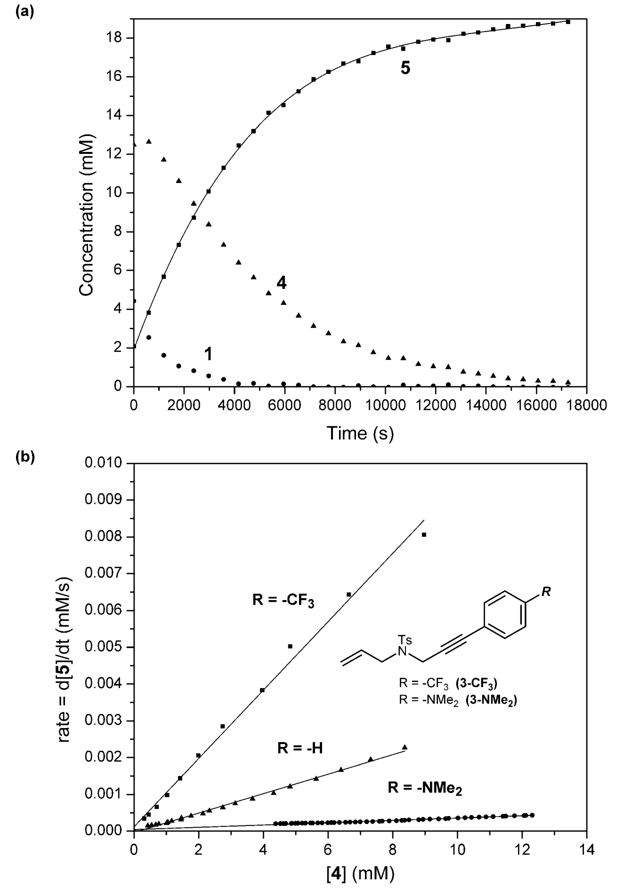


Figure 4. a) Kinetic profile for the reaction between complex **1** and enyne **3** to form the metallacycle **5** (monitored by ^{1}H NMR spectroscopy, 30 °C). b) First-order dependence of d[**5**]/d*t* on [**4**].

metal center. In accordance with this description, there is a rate increase for the more electron-deficient CF_3-substituted substrate and a decrease for the NMe_2-substituted enyne. A plot of the first-order rate constants as a function of the Hammett σ_p constants yields a ρ value of $+0.88$, indicating a buildup of negative charge at the C2 position in the transition state.[16]

A central question regarding the electronic structure of the key Pauson–Khand intermediates is the relative distribution of redox activity between the two metal centers, the supporting ligands, and the fragments undergoing coupling. In the case of the $[NDI]Ni_2$-mediated reaction, calculations suggest that a significant redistribution of electron density occurs in the initial ligand substitution process. Loss of C_6H_6 and coordination of the alkyne is accompanied by charge transfer from the NDI π system to the bound alkyne (0.20 electron equivalents by NBO population analysis), resulting in an activation of the C−C triple bond (1.334(2) Å in complex **2**). The subsequent coupling then proceeds with minimal change in the partial charges of either the NDI ligand or the Ni−Ni bond. These calculated values are reflected experimentally in the bond metrics associated with the redox-sensitive NDI π system. It is noteworthy that previous DFT calculations conducted on the $Co_2(CO)_8$ system also indicated a valence isoelectronic d^9–d^9 Co^0–Co^0 state for the analogous alkyne and metallacycle complexes.[8a] By this analysis, the alkene–alkyne coupling step is better formulated as a redox-neutral migratory insertion rather than a two-electron oxidative coupling.

Having demonstrated an efficient dinuclear alkene–alkyne coupling pathway, we next evaluated whether analogous reactivity is observed using mononickel complexes. Ni metallacycles formed from the coupling of an alkyne and a hetero π component (for example, imines and α,β-unsaturated aldehydes) are known,[17] but those specifically derived from an alkyne and an unactivated alkene have not previously been reported.[18] Accordingly, we surveyed the reactivity of enyne **3** with a range of [*N,N*]Ni(COD) complexes bearing iminopyridine, bipyridine, and diazadiene (DAD) chelates. Complexes of the former two ligand classes yielded only intractable product mixtures, characterized by the formation of insoluble precipitates. Fortuitously, the $[^{i\text{-Pr}}DAD]Ni(COD)$ complex **7** afforded well-defined reactivity, enabling the mononickel coupling pathway to be characterized.

Complex **7** undergoes ligand exchange with **3** to form the alkyne adduct **8** (Figure 5 a). No further reactivity is detected, even after heating at 60 °C for 3 days. However, the more reactive CF_3-substituted enyne is competent at undergoing C−C coupling, albeit in low yield and at a significantly slower rate than the dinuclear process. The reaction reaches full conversion after 12 h at 60 °C, providing the metallacycle **9**-CF_3, which was isolated in a yield of 18 % after crystallization, along with a mixture of unidentified side products. The most notable difference between the structure of **9**-CF_3 (Figure 5 b) and its dinickel congener, **5**, is the absence of the η^2 Ni–π interaction. Consequently, the carbons belonging to the alkenyl group are sp^2-hybridized, positioning the C2 substituent roughly in the plane of the five-membered ring. This structural contrast highlights a key element of stereocontrol in the proposed mechanism of the Pauson–Khand reaction, wherein the metal–metal bond imparts stereogenicity at the

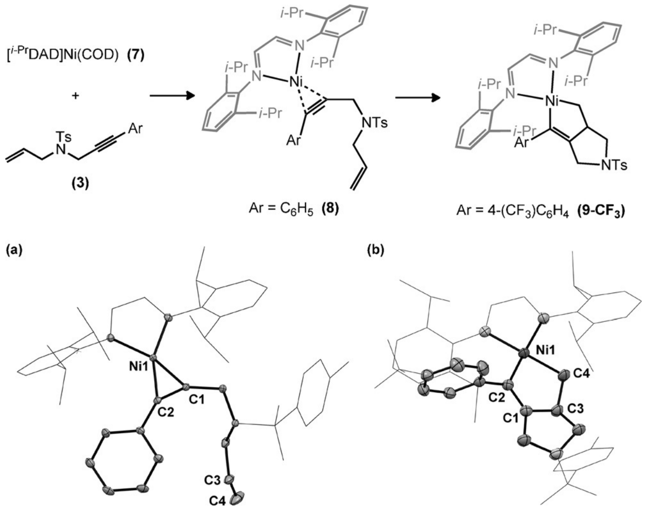


Figure 5. Top: Mononickel alkene–alkyne coupling reactions. Bottom: Solid-state structures of a) **8** and b) **9**-CF_3. Thermal ellipsoids in (a) and (b) are at 50 % probability.

C1 and C2 positions, which, in turn, influence the configuration of the newly forming center at the C3 position.

In summary, the [NDI]Ni_2 platform serves as a functional model for $Co_2(CO)_8$ in the Pauson–Khand reaction, providing insight into key intermediates that are otherwise thermodynamically inaccessible. The Ni–Ni bond presents a unique electronic environment for alkene–alkyne coupling reactions, facilitating metallacycle formation through a stabilizing secondary Ni–π interaction. This interaction is notably absent in the mononickel pathway, which proceeds at a substantially slower rate and in low yield. In addition to addressing unresolved questions regarding the mechanism of the classic Pauson–Khand reaction, these results underscore the opportunities for controlling the activity and selectivity of cycloaddition catalysts by manipulating the number of metal centers in the active site.

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