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Metal–Organic Proximity in a Synthetic Pocket

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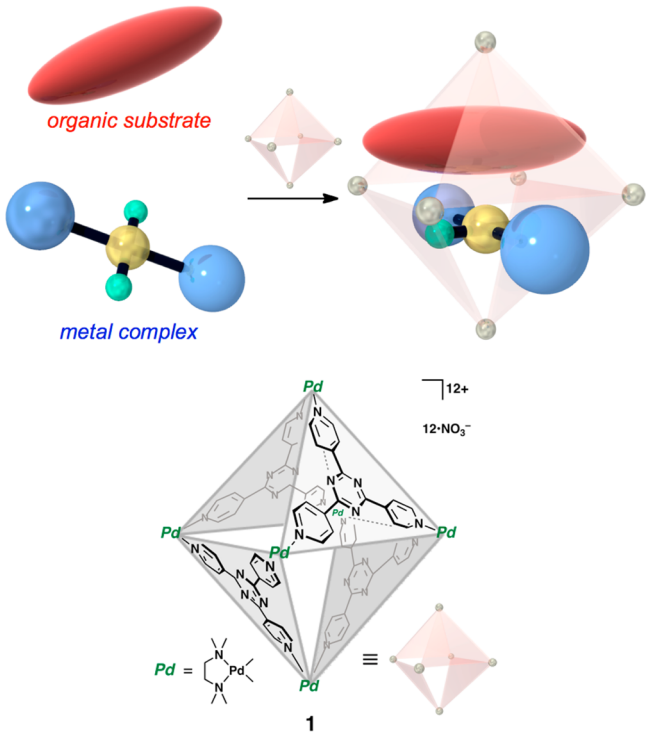
Supporting Information

ABSTRACT: Proximity between a noninteractive organic substrate and a transition metal (*trans*-$MCl_2(PEt_3)_2$; M = Pd or Pt) is achieved by their co-encapsulation within a synthetic cage, as revealed by X-ray crystallographic analysis and NOESY experiments. Through co-encapsulation with a Pd(II) complex, a terminal alkyne was activated within the cage to give a σ-alkynylpalladium complex.

Metalloenzymes bring substrates close to the embedded metal in the binding pocket in order to perform efficient and specific chemical transformations under ambient conditions.[1] In this report, we established the similar proximal states between a Pt(II) or Pd(II) complex and various organic substrates by accommodating them in the pocket of a synthetic cage. X-ray single-crystal diffraction and NMR analysis revealed the closely packed conformation of the guest pairs within the cage. This method is of great potential and promising because the construction of a metal–organic pair depends not on the intrinsic interaction between them but on the shape complementarity of the pair to the interior cavity: saturated hydrocarbons are paired with the metal complexes despite negligible interactions between them.[2] In addition, the close proximity of the Pd(II) complex and a terminal alkyne promoted C(sp)–H activation to form a σ-alkynylpalladium(II) complex in the cavity.[3] This activation occurs without the help of a Brønsted base and even under acidic conditions. Furthermore, the cage architecture exhibited shape selection in the terminal alkyne activation, reminiscent of events in metalloenzymes.

Self-assembled host cages are able to bind two organic guests in a pairwise selective fashion[4] and subsequently promote the thermal and photochemical reactions[5] of the paired guests. In contrast to organic guests, sterically demanding metal complexes have rarely been bound by host cages.[6] In particular, the pairwise selective binding of metal complexes with an organic guest has seldom been achieved. Bergman and Raymond have reported the C–H activation of aldehydes in their M_4L_6 "nanozyme" cage, in which the co-encapsulation of an Ir(III) complex with an aldehyde is considered.[6f,7] Herein, the pairwise selective guest recognition by self-assembled M_6L_4 cage **1** is applied to the co-encapsulation of a metal and an organic substrate within a host cage (Scheme 1). We found that square planar complexes, *trans*-$MCl_2(PEt_3)_2$ (M = Pd or Pt), are tightly co-encapsulated with various linear organic guests within cage **1**. If the organic guests are terminal alkynes, they are able to react with the Pd(II) complex under neutral or even acidic conditions to give Pd(II)–C≡C–R complexes. The guest shapes are recognized by the cage in the C(sp)–H activation process. As a result, the synthetic cage operates a shape-selective C(sp)–H activation in a similar way to that of enzymatic reactions.

Scheme 1. Cartoon Representations of the Pairwise Encapsulation of a Metal Complex and an Organic Substrate into Self-Assembled M_6L_4 Cage 1



Of the several square planar Pd(II) or Pt(II)–phosphine complexes tested, the sterically undemanding *trans*-$MCl_2(PEt_3)_2$ (**2a**: M = Pt, **2b**: M = Pd) were efficiently accommodated in the cavity of **1**. Complex **2a** was suspended in an aqueous solution of cage **1** (5 mM) at room temperature for 5 h. After removing excess **2a** by filtration, ^{1}H NMR spectroscopy confirmed the formation of inclusion complex **1**·**2a** in 97% yield (Figure 1c). Upon inclusion, the ethyl signals of **2a** are shifted upfield by approximately 1.8 ppm, but the cage signals are qualitatively the same as those of the empty cage. The tetrahedral symmetry of the cage, which persists after guest inclusion, indicates the loose packing of the guest. The 1:1

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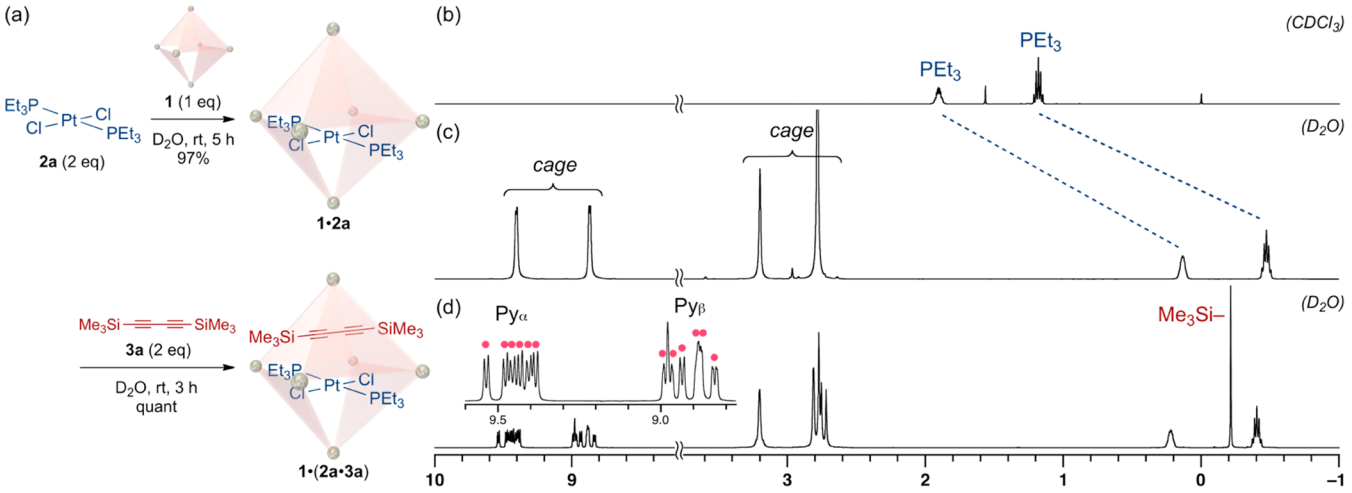

Figure 1. (a) Formation of inclusion complex **1**·**2a** and ternary complex **1**·(**2a**·**3a**). ^{1}H NMR spectra (500 MHz, 300 K) of (b) **2a** in $CDCl_3$, (c) **1**·**2a** in D_2O, and (d) **1**·(**2a**·**3a**) in D_2O.

host–guest stoichiometry was confirmed by the NMR integral ratios. Subsequently, diyne **3a** was added to the solution of **1**·**2a**, and the suspension was stirred at room temperature for an additional 3 h. After filtration of excess **3a**, the quantitative formation of the 1:1:1 ternary complex, **1**·(**2a**·**3a**), was revealed by ^{1}H NMR spectroscopy (Figure 1d). This ternary complex was also obtained quantitatively in a one-pot encapsulation procedure (see the Supporting Information).

In addition to the ethyl signals of **2a**, the signal from the trimethylsilyl (TMS) group of co-encapsulated **3a** was also shifted upfield. The pyridyl signals of **1** were split into six sets, which is consistent with the reduction of cage symmetry from T_d to C_{2v}.[8] The NOESY spectrum of **1**·(**2a**·**3a**) shows a clear correlation between the TMS signal of **3a** and half of the six pyridyl groups of **1** (see Figure S4a). The other half of the pyridyl groups are correlated with the ethyl groups of complex **2a**. These observations indicate that the cage restricts the free motion of the guest pair in order that the C_{2v} symmetric orthogonal arrangement of the two guests can be adopted. The bulky parts of diyne **3a** and complex **2a** are expected to lie at the portals of the cavity in order to efficiently fill the available space.

All of these NMR observations fully agree with the crystal structure of the **1**·(**2a**·**3a**) complex (Figure 2). The crystal structure illustrates the close-packing of the two guests with an orthogonal arrangement of their molecular axes. Namely, the PEt_3 ligands of **2a** and the TMS groups of **3a** are located at the portals of the octahedral cage. The distances between the Pt(II) center and the central *sp*-carbon atoms of **3a** are 5.31 and 5.32 Å (see Figure S13a), considerably larger than the sum of their van der Waals radii (3.75 Å).[9] The two bulky groups (TMS and PEt_3) seem to prevent the tight contact between the Pt(II) and alkyne sites and any subsequent reactions between them.

In addition to **3a**, various linear organic molecules were efficiently and selectively co-encapsulated within the cavity of **1** with complexes **2a**,**b** (Table 1). Both **2a** and **2b** showed similar co-encapsulation yields with the other organic substrates **3**. The linear shape of the substrate was essential to the pairwise selective encapsulation. Linear diyne **3c** and monoyne **3d** were also accommodated in cage **1** in excellent yields (89–97%, entries 3,4). Linear *trans*-olefin **3e** is also a good substrate, but bent *cis*-olefin **3f** did not form the ternary complex, probably due to its poor fit to the cavity (entries 5,6). More flexible *n*-alkane **3g** was only accommodated in low yields (27–41%, entry 7), but interestingly, *α*,*ω*-dibromoalkane **3h** formed ternary complex **1**·(**2**·**3h**) in 91–93% yield (entry 8). This is most likely due to the increased solvation of the substrate at the portals of the cage in water,[8,10] which results from the polar C–Br bonds at both ends of **3h**. The efficient binding of saturated hydrocarbons **3g**,**h** indicates that the co-encapsulation can be ascribed to the shape complementarity and not to the inherent interaction between the two guests. Monoyne **3b** was not co-encapsulated (entry 2), presumably because the two TMS groups in **3b** inevitably cause steric repulsion with the triazine panels of cage **1**.

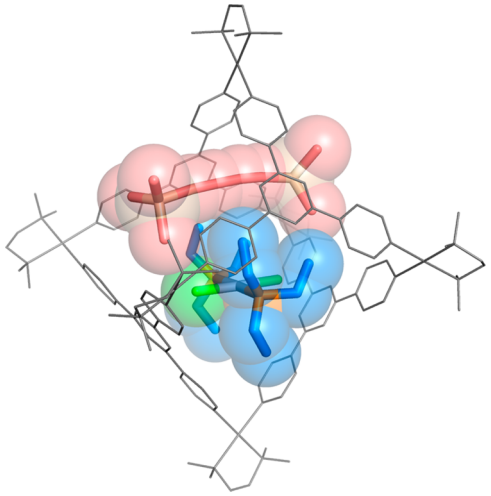

Figure 2. X-ray crystal structure of **1**·(**2a**·**3a**). For clarity, only one of the disordered positions of the ethyl group is shown. See the Supporting Information for details.

We expected a significantly closer proximity between the metal and the substrate, and the consequent activation of the substrate, if the sterically bulky groups on the substrate were removed. Thus, the pairwise encapsulation of terminal alkyne **3i** with Pt(II) complex **2a** was examined (Figure 3). NMR analysis revealed the formation of ternary complex **1**·(**2a**·**3i**) in 79% yield. In anticipation of the subsequent activation of **3i**, more labile Pd(II) complex **2b** was subjected to the co-encapsulation under the same conditions. Surprisingly, the observed product

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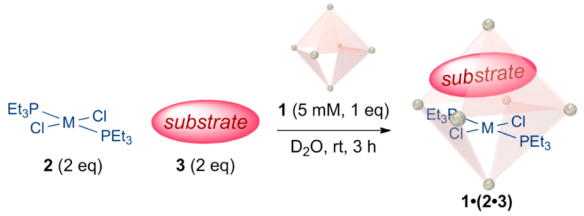
Table 1. Pairwise Encapsulation of Complex 2 and Organic Substrate 3



Entry	3	Yield (%)[a] 1•(2a•3)	Yield (%)[a] 1•(2b•3)
1[b]	Me_3Si—≡—≡—$SiMe_3$ **3a**	quant	quant
2	Me_3Si—≡—$SiMe_3$ **3b**	0	0
3	**3c**	98	97
4	**3d**	89	93
5	**3e**	58	41
6	**3f**	0	0
7	**3g**	41	27
8	Br—Br **3h**	91	93

[a]The encapsulation yields were calculated from the integral ratio of the guest to the cage. [b]6 h.

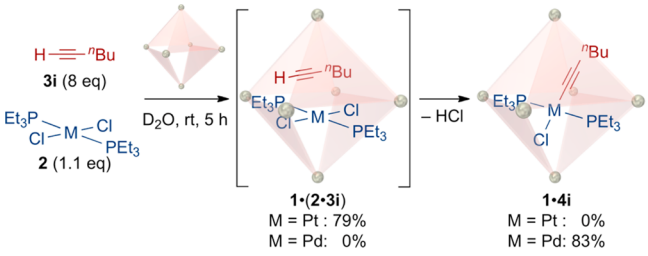


Figure 3. Cavity-promoted C(sp)−H activation of terminal alkyne **3i** with Pd(II) complex **2b**.

was not ternary complex **1**·(**2b**·**3i**), but inclusion compound **1**•**4i** (83%), in which σ-alkynylpalladium complex **4i** was presumed to have formed through terminal C−H activation of **3i** by **2b** in the cavity of cage **1**.[11] A control reaction without the cage gave none of condensation product **4i**, and Pd(II) complex **2b** and terminal alkyne **3i** remained unreacted in the THF/D_2O (9:1) solution.[12] We also found that diyne substrate **3a**, which forms stable ternary complex **1**·(**2b**·**3a**), inhibited the reaction. Namely, treatment of **3i** with **1**·(**2b**·**3a**) under the same conditions afforded **1**·**4i** in only 19% yield, and ternary complex **1**·(**2b**·**3a**) was recovered in 72% yield. These experiments show that terminal alkyne **3i** was activated by encapsulated **2b**, not by liberated **2b** in solution, and clearly reveal that the close proximity of **2b** and **3i** within the cavity of **1** is crucial for the reaction to take place.

It is noteworthy that the reaction solution became acidic during the reaction due to the generation of hydrochloric acid. Even if the reaction was performed under acidic conditions from the start (pH = 3.2), C(sp)−H activated product **1**·**4i** was formed in 66% yield (pH = 2.1 after the reaction). Thus, a simple base-mediated deprotonation mechanism[3] for the formation of the σ-alkynylpalladium complex must be excluded. Presumably, direct C(sp)−H activation occurs between the two guests in the secluded cavity.[13]

The shape complementarity of the two guests is again a dominant factor for efficient C(sp)−H activation. Whereas linear alkyne **3j** showed moderate reactivity (66%), the yield of the reaction with *tert*-butyl-containing alkyne **3k** was considerably inferior (10%, Figure 4), even though the inherent reactivity of the terminal C−H bond is comparable between the two substrates.[14]

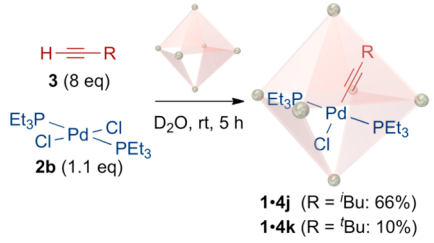


Figure 4. Shape-selective C(sp)−H activation of terminal alkyne **3** with Pd(II) complex **2b**.

In summary, we succeeded in the pairwise selective recognition of a transition metal complex with various linear organic compounds in the cavity of a self-assembled coordination cage. The paired guests are rendered in close proximity within the cavity, and in the case of terminal alkynes with a Pd(II) complex, the C(sp)−H bond is activated to give Pd(II)−C≡C−R. This cavity-controlled alkyne activation may lead to a general method for C−H activation, suitable even for sp^2 and sp^3 carbon atoms, that does not require the aid of any directing group on the substrates. It is expected that the control of the regiospecificity of the reactions through the design of precise molecular recognition, and the development of catalytic cycles will offer an ultimate method for C−H activation, equal to that of metalloenzymes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, physical properties, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) Ternary complex **1**·(**2a**·**3i**) was stable over 2 days, and no reaction proceeded inside the cage.

(12) A control experiment with Pd(tmeda)$(NO_3)_2$ afforded a complex mixture of poorly characterized constituents.

(13) We now assume a concerted direct dehydrochlorination mechanism between the two guests in the secluded cavity.

(14) The reactions are regulated at the stage of guest encapsulation because the co-encapsulation yields of **1**·(**2a**·**3i**−**k**) are well correlated with the reaction yields of **1**·(**4i**−**k**) (see Table S3 in Supporting Information).