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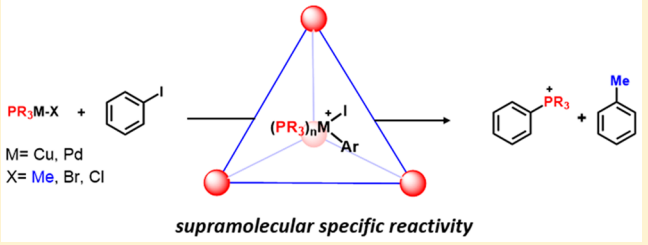
Supramolecular Host-Selective Activation of Iodoarenes by Encapsulated Organometallics

Trandon A. Bender,[‡] Mariko Morimoto,[‡] Robert G. Bergman,* Kenneth N. Raymond,* and F. Dean Toste*

Chemical Sciences Division, Lawrence Berkeley National Laboratory, and Department of Chemistry, University of California, Berkeley, California 94720, United States

Supporting Information

ABSTRACT: Supramolecular hosts offer defined microenvironments that facilitate selective host−guest interactions, enabling reactivity that would otherwise be challenging in bulk solution. While impressive rate enhancements and selectivities have been reported, similar reactivity can often be accessed through modifications of reaction conditions even in the absence of the host. We report here an oxidative addition of aryl halides across the metal centers in Cu(I) and Pd(II) organometallics that is assisted by the presence of a supramolecular host, realized via electrostatic stabilization and increased local substrate concentrations. When reaction conditions were screened to assess background reactivity, alternative reactivity (typically decomposition) resulted, indicating that encapsulation led to host-selective reaction trajectories.



INTRODUCTION

Advances made at the interface of organometallic chemistry and microenvironment catalysis have broadened the scope and relevance of supramolecular strategies in synthetic chemistry.[1−11] Notable examples include allylic alcohol isomerizations,[12,13] hydroformylations,[14,15] and alkyne hydrations.[16] However, examples of transformations that are supramolecular host-selective are rare in a growing field, where applications typically involve accelerating reaction rates and/or improving selectivities from those conducted in bulk solution. For example, we have previously shown that the M_4L_6 Raymond tetrahedron (**1**) accelerates the reductive elimination of ethane from a Au(III) complex by more than a million-fold (Figure 1).[9]

Despite the impressive rate acceleration achieved with **1**, reductive eliminations from high-valent gold complexes have been shown to proceed at a comparable rate even in the absence of the host. Thus, overcoming background reactivity is one of the most challenging aspects in organometallic transformations promoted by supramolecular hosts. Similar reactivity in the absence of supramolecular influence indicates that the host remains selective for a lowest energy reaction pathway. Therefore, demonstrating a transformation in which the host not only accelerates but alters the lowest energy reaction pathway from that in bulk solution would be an intriguing step forward for the field, as very few examples are known.[17]

The dearth of examples where a supramolecular host "turns on" distinct reactivity for an organometallic transformation presents an opportunity to identify a reaction that is typically not facile under traditional organic and host (aqueous) conditions. Moreover, modifying reaction conditions (elevated temperature, additives, etc.) to assess divergent reactivity would further demonstrate that the selected reaction is a cage-specific transformation. Although not obvious *a priori*, we discovered that the Cu(I)/(III)[18] and Pd(II)/(IV)[19] oxidative addition/reductive elimination cycles with iodoarenes are excellent candidates to perform such an investigation.

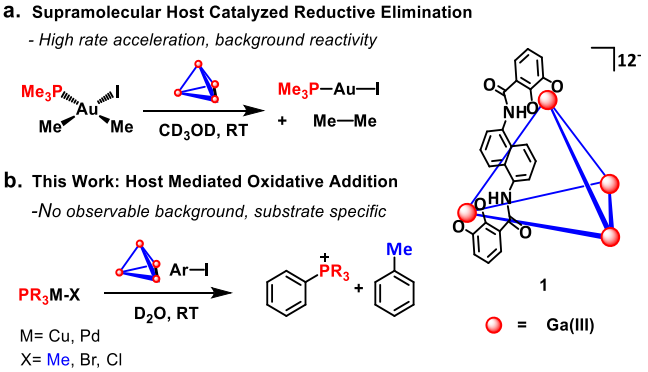


Figure 1. (a) Previously reported cage-accelerated reductive elimination. (b) This work: cage-mediated oxidative addition of iodoarenes under mild conditions.

RESULTS AND DISCUSSION

We first investigated the ability of a simple 1,2-bis-(dimethylposphino)ethane (DMPE)−copper complex

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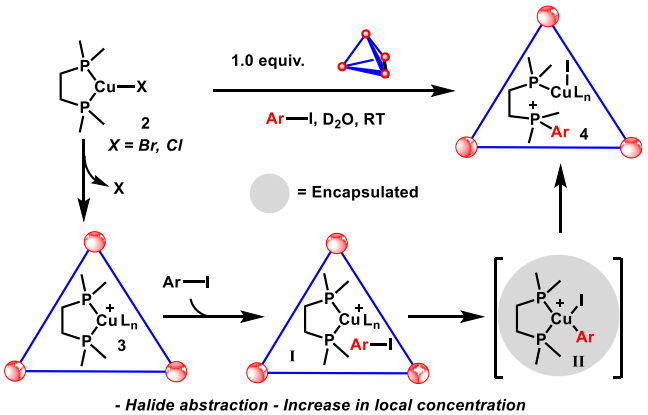
((DMPE)CuBr, **2**; Scheme 1) to undergo iodoarene carbon–iodine oxidative addition. Although this copper–phosphine

Scheme 1. Proposed M_4L_6-Mediated Mechanism for Formation of Asymmetric Aryl Phosphonium 4



complex is an atypical catalyst for traditional Ullmann-type coupling reactions, it proved to be an ideal species for this investigation due to its high stability under aqueous conditions, which arises from its low solubility in water. In contrast, the amine-ligated analogues rapidly disproportionated in aqueous media, rendering direct comparison between the host-mediated system and the potential background organometallic reaction spectroscopically challenging. Due to the low solubility of **2**, no reactivity was observed upon combination with iodobenzene in water, even after long reaction times and heating. More interesting still is the lack of reactivity in conventional organic solvents (such as methylene chloride and acetonitrile), where both **2** and iodobenzene are fully soluble.

Given these negative controls in both aqueous and organic media, we sought to determine if reactivity was possible under the influence of supramolecular host **1**. It has been demonstrated previously that **1** functions as a halide abstractor toward neutral organometallics, promoting encapsulation of the resulting cationic species.[10] Combining a small excess of **2** with **1** resulted in a heterogeneous mixture. Removal of remaining solid by filtration after 30 min yielded a 1:1 host:guest complex, as indicated by diagnostic upfield shifted resonances for encapsulated **3** (Figure 2a).

Addition of iodobenzene to **3** resulted in new upfield shifts in the ^{1}H NMR spectrum corresponding to simultaneous encapsulation of the copper complex and iodobenzene (**I**, Figure 2b).[20−22] Over the course of 12 h at room temperature, full conversion of the starting material to a new product was observed with concomitant loss of symmetry in both encapsulated **3** and the host (Figure 2c). A 2D NOESY experiment of the product indicated correlation between the aromatic peaks and one set of DMPE methyl peaks. This observation provided initial support for copper phosphonium **4**, where an aryl-dimethylphosphonium ion had formed at one phosphine, while the other remained coordinated to the copper center (by analogy to the $\{^1H\}^{31}P$ shift of the starting material).[23] Further evidence of an aryl phosphonium copper(I) species was obtained by independently preparing ethyldimethyl (phenyl)phosphonium **5** (see Supporting Information, p S6) and subjecting it to the M_4L_6 assembly. The $\{^1H\}^{31}P$ NMR shift of the encapsulated phosphonium **5** was identical to that of one of the phosphine signals of the asymmetric DMPE backbone of aryl phosphonium copper species **4**. Lastly, electrospray ionization mass spectrometry (ESI-MS) confirmed encapsulated **4**, predominantly detected in the −3 and −4 charge states (see Supporting Information, p S22), verifying that the species is monocationic, with the iodide (from iodobenzene) still ligated to copper.

While the resulting Cu(I)–I phosphonium product (**4**) was unexpected, it implies room-temperature carbon–iodine oxidative addition with encapsulated **3** followed by rapid aryl–phosphine reductive elimination via a putative Cu(III) intermediate (**II**, Scheme 1). Lack of reactivity in control studies indicated that reaction progress is specific to cage **1** and raises the question as to the exact role of the host in this transformation and whether the same reactivity could be

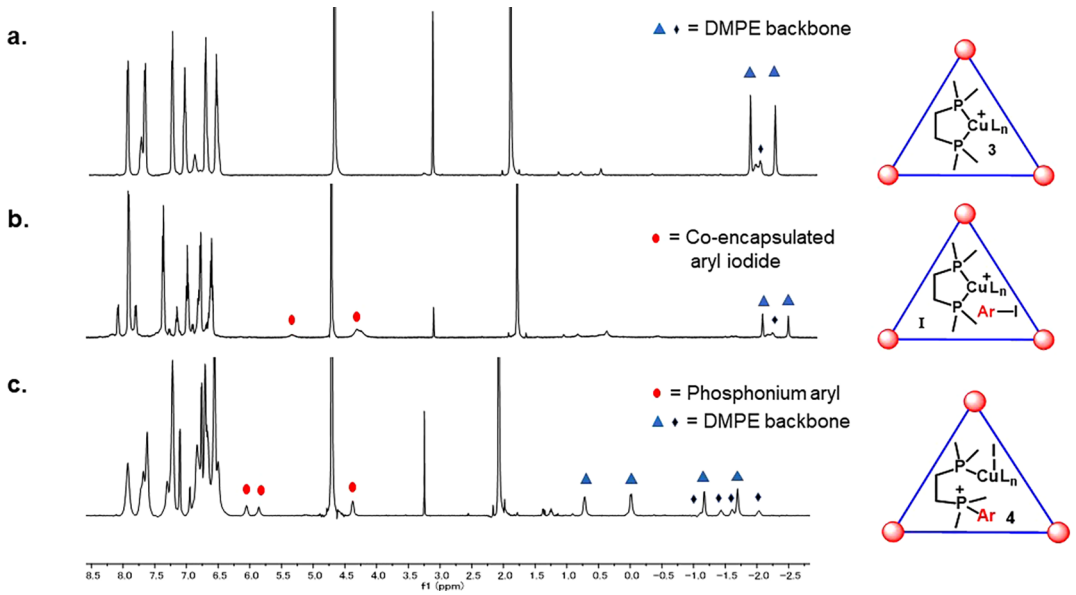


Figure 2. (a) Encapsulation of copper(I) complex **3** in a 1:1 host:guest ratio determined by ^{1}H NMR (500 MHz, 25 °C). (b) Coencapsulation of aryl iodide and **3**.[20] (c) Encapsulated product **4** after oxidative addition and rapid reductive elimination of iodobenzene.

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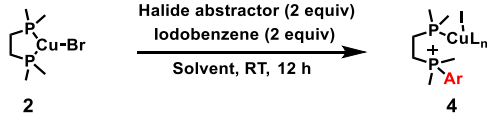
observed with an exogenous halide abstractor. To this end, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBAr^F) was investigated as a model halide abstractor for this transformation (Table 1).

Table 1. Reaction Conditions and Results for Control Experiments



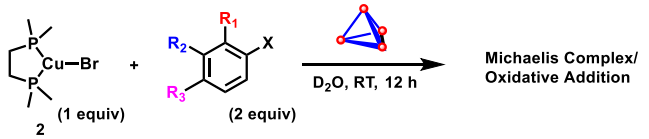
2 4

entry	halide abstractor	solvent	product 4
1	NaBAr^F	D_2O	trace
2		D_2O	no conversion
3	NaBAr^F	DCM	complex mixture
4		DCM	no conversion
5	NaBAr^F	MeCN	no conversion
6		MeCN	no conversion

Copper complex **2**, iodobenzene, and 2 equiv of NaBAr^F were combined in water. The solubility of the starting complex improved slightly, and monitoring over extended times resulted in trace **4** by $\{^1H\}^{31}P$ NMR, while no reactivity was observed with addition of NaBAr^F to **2** in acetonitrile. A mixture of products was observed when the reaction was conducted in dichloromethane; however, after removal of solvent from this reaction and addition of **1** in D_2O, no encapsulated phosphonium species were observed, suggesting that **4** was not present in the crude reaction mixture. Furthermore, addition of 2 equiv of iodobenzene to DMPE in refluxing benzene resulted in no reactivity over extended reaction times, verifying the participation of copper in phosphonium formation. Taken together, these data demonstrate that host **1** is uniquely selective for this transformation and different approaches result in either trace to no conversion or nonproductive (decomposition) reactivity.

To further explore the generality of the above reactivity, additional substrates were screened for oxidative addition/reductive elimination with encapsulated **3**. This screening indicated that stabilization of Cu(I) cation **3** within **1** was not the only factor responsible for the observed reactivity. For instance, oxidative addition with aryl halide substrates bearing *para*-electron-donating and -withdrawing substituents gave no conversion (Table 2, entries 2, 3). Insight was gleaned, however, upon investigating iodotoluene substrates (Table 2, entries 4–6). Combining *para*-iodotoluene with encapsulated **3** did not result in coencapsulation or new reactivity, as evidenced by ^1H NMR spectroscopy. Coencapsulation of *meta*-iodotoluene was also not observed; however, starting material was slowly consumed and resulted in the formation of the analogous phosphonium product with heating (50 °C, 12 h), suggesting that this substrate undergoes rapid ingress/egress.[24] *ortho*-Iodotoluene showed coencapsulation as observed with iodobenzene, but no subsequent reactivity at room temperature. As with *meta*-iodotoluene, warming the reaction mixture resulted in full conversion to the analogous phosphonium salt.

Table 2. Investigating Oxidative Addition Protocol with Alternative Substrates



entry	X	R_1	R_2	R_3	Michaelis complex/oxidative addition
1	Br	H	H	H	observed, no conversion
2	I	H	H	F	not observed, no conversion
3	I	H	H	OMe	not observed, no conversion
4	I	H	Me	H	not observed, full conversion[a]
5	I	H	H	Me	not observed, no conversion
6	I	Me	H	H	observed, full conversion[a]

[a]Reaction performed at 50 °C.

From this it is found that in the case of *para*-substituted iodotoluenes (Table 2, entries 3 and 4) no Michaelis complex is observed along with no detectable conversion due either to poor guest encapsulation or to steric encumbrance of the elongated substrate. Furthermore, *meta*-iodotoluene (Table 2, entry 4) reacts sluggishly (12 h at 50 °C) without the observation of a Michaelis complex, indicating more favorable exchange or steric profile. However, when a defined Michaelis complex is observed, reactivity under mild conditions (12 h at RT) proceeds as in the case of iodotoluene. An exception is when substrate steric hindrance occurs, as is the case with *ortho*-iodotoluene, requiring more forcing conditions (12 h at 50 °C).

This reactivity is congruent with previous reports demonstrating that two substrate molecules of iodobenzene and *ortho*-iodotoluene encapsulate within **1**, whereas only a single molecule of *meta*- and *para*-iodotoluene can be accommodated, consistent with the hypothesis that reactivity is specific to strongly bound guests.[25] Furthermore, it is worth noting that although *para*-iodotoluenes are more reactive toward oxidative addition than *ortho*-iodotoluenes under traditional organic conditions, this trend is reversed under host-mediated conditions. Confinement within the host thus not only enables iodoarene activation under unusually mild conditions but also gives rise to atypical selectivities due to differential guest binding.

In light of these results, we sought to demonstrate that host stabilization of a cationic organometallic species in the presence of a good organic guest could facilitate another transformation contingent upon the presence of **1**. The Pd(II)/Pd(IV) oxidative addition/reductive elimination cycle with iodoarenes was selected as a challenging but interesting manifold to investigate. Initial studies were conducted with (DMPE)Pd(II)MeCl, which, analogously to Cu complex **2**, was quantitatively encapsulated within the host as the monocationic species (see Supporting Information, p 7). Upon addition of iodobenzene to the host-encapsulated DMPE Pd(II)Me cation, rapid conversion of the encapsulated species was observed by ^1H NMR spectroscopy. Analysis of the extracted reaction mixture revealed trace amounts of toluene, a product expected from oxidative addition/reductive elimination of the methyl and aryl ligands. The control reaction in the absence of host, however, demonstrated significant background reactivity, presumably due to solubility and stability of (DMPE)Pd(II)MeCl in water. Attributing this stability to the strongly coordinating bidentate phosphine ligands, monodentate PEt_3 Pd dimer **6** was investigated.

The lack of solubility of **6** in water resulted in no reactivity with iodobenzene in a background control reaction. Utilization of a halide abstractor (NaBAr^F) resulted in rapid decom-

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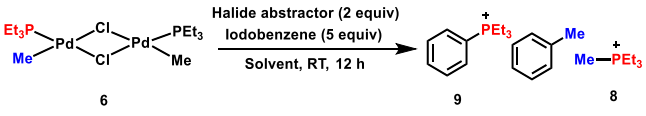
position to palladium black with no iodobenzene activation. Despite significantly improved solubility in dichloromethane, no reaction was observed between iodobenzene and **6**, and heating (100 °C) eventually resulted in decomposition. Addition of a halide abstractor to the reaction mixture in dichloromethane resulted in rapid decomposition, which again precluded reactivity with iodobenzene (Table 3).

Table 3. Reaction Conditions and Results for Control Experiments



6 9 8

entry	halide abstractor	solvent	result
1	$NaBAr^F$	D_2O	Pd(0), trace **8**
2		D_2O	no conversion
3	$NaBAr^F$	DCM	Pd(0), trace **8**
4		DCM	no conversion

Combining palladium dimer **6** with the host provided quantitative encapsulation of a unique monomeric cationic Pd species **7** (Figure 3a). In analogy to our observations using Cu complex **2**, it is proposed that dimer cleavage and palladium uptake by the host occurs with concomitant loss of chloride to yield a stabilized palladium cation, which is presumably solvated within the host. Upon addition of iodobenzene (5 equiv), encapsulated **7** was consumed, and two distinct species formed. The identity of the products, **8** and **9**, was verified by direct analogy to authentically prepared phosphonium salts. The generation of these products is indicative of iodoarene oxidative addition and subsequent Csp^3–P or Csp^2–P reductive elimination to give **8** and **9**, respectively. In addition to phosphonium products, toluene was detected by ^1H NMR spectroscopy and GC/MS analysis upon workup, thus supporting the intermediacy of a putative Pd(IV) complex that can also undergo Csp^2–Csp^3 reductive elimination.

As the Pd(0)/Pd(II) redox cycle may also be a possible mechanism for the production of the species observed above, additional control experiments were performed to determine if this cycle was operative. Generation of encapsulated **8** and palladium black occurs without the addition of iodobenzene over extended times. Since reductive elimination provides a source of Pd(0) that, although very insoluble, could result in Pd(0) reactivity and subsequent product formation, additional control experiments were performed. A sample of **7** was allowed to stand for 24 h, yielding full conversion of the starting material to Pd(0) and encapsulated **8**. Introduction of iodobenzene to this mixture resulted in no formation of **9**, and only residual iodobenzene was detected by ^1H-NMR or GC/MS analysis, suggesting that oxidative addition/reductive elimination is occurring within host **1** from a Pd(II) species.

In conclusion, the ability of supramolecular host **1** to stabilize a reactive cationic organometallic in the presence of a well-encapsulated iodoarene guest has demonstrated reactivity that occurs selectively within the host cavity. The observation that oxidative addition with simple Cu(I) and Pd(II) salts occurs under mild conditions in water illustrates that supramolecular cages can provide access to host-selective reaction trajectories.

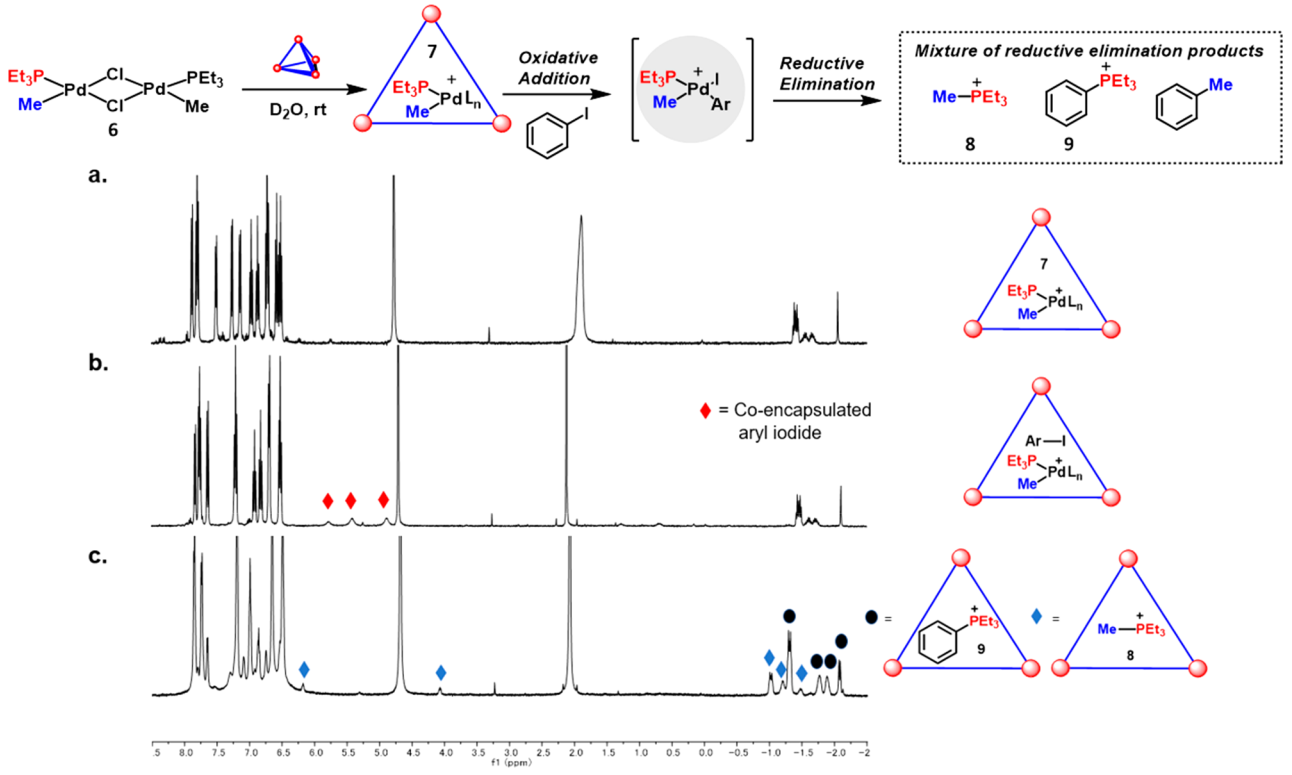


Figure 3. (a) ^1H NMR analysis (500 MHz, 25 °C) of palladium(II) monomer **7** encapsulated in host **1**. (b) Coencapsulation of aryl iodide and **7**. (c) ^1H NMR analysis after addition of iodobenzene, indicating encapsulation of phosphonium products **8** and **9**.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b11842.

General synthetic procedures, ESI-MS data, and characterization of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*rbergman@berkeley.edu
*raymond@socrates.berkeley.edu
*fdtoste@berkeley.edu

ORCID

F. Dean Toste: 0000-0001-8018-2198

Author Contributions

‡T. A. Bender and M. Morimoto contributed equally.

Notes

The authors declare no competing financial interest.

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(20) Detection of coencapsulated iodobenzene and copper species **3** proved challenging due to exchange and faster reaction times. However, direct NOE correlation of an analogous substrate, *ortho*-iodotoluene, and copper species **3** was observed. See Supporting Information for experimental details.

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