Supramolecular Chemistry

Selective C–H Bond Activation by a Supramolecular Host–Guest Assembly**

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The development of synthetic supramolecular compounds that mimic enzyme catalysts with well-defined internal environments represents a novel approach to improving the ability to control the rate and selectivity of organometallic reactions. Rather than using many different inner-sphere ligands to effect changes in reactivity, the outer-sphere environment of a self-assembled host cavity may be used to introduce new types of size and shape selectivity. A number of such synthetic "nanovessels" have been reported and their ability to encapsulate organic guests has been investigated.[1–5] While a number of thermal and photochemical organic transformations have been performed inside some of these nanovessel cavities,[6–9] there are very few reports on the encapsulation of reactive metal complexes in such host assemblies and their resultant reactivity.[10–13] We have recently shown that a synthetic supramolecular nanovessel can induce high diastereoselectivies in the encapsulation reactions of chiral guests.[14] We report herein the first supramolecular encapsulations and reactivity studies of organometallic complexes, in the specific context of carbon–hydrogen bond activation, in a self-assembled nanovessel host cavity.

Raymond and co-workers have reported the formation and host–guest properties of supramolecular tetrahedral assemblies of $[M_4L_6]^{12-}$ stoichiometry (M = Ga^{3+}, Al^{3+}, Fe^{3+}; L = bis(bidentate) catecholamide).[15] These structures are formed through the self-assembly of achiral components to yield exclusively a racemic mixture of homochiral Δ,Δ,Δ,Δ- or Λ,Λ,Λ,Λ-clusters with Δ or Λ configuration at each metal center. One such $[Ga_4L_6]^{12-}$ assembly utilizes a naphthalene-based catecholamide ligand backbone (Figure 1). This highly negatively charged capsule is soluble in polar solvents, such as water, but the naphthalene-based ligand scaffold generates a hydrophobic cavity of approximately 0.5 nm^3. This hydrophobic cavity allows the assembly to encapsulate a variety of hydrophobic monocationic species,[16] for example, organic cations, such as $[NMe_4]^+$ and $[NEt_4]^+$, as well as organometallic sandwich complexes, such as $[Cp_2Fe]^+$, $[Cp_2Co]^+$, and $[CpRu(C_6H_6)]^+$ (Cp = η^5-C_5H_5).[11,17,18] This supramolecular host was initially prepared in the presence of NMe_4Cl to form $[Na_4(NMe_4)_7][NMe_4{\subset}Ga_4L_6]$ (⊂ denotes guest encapsulation within host), which helps to stabilize the tetrahedral assembly during its formation. The $[NMe_4]^+$ cation binds weakly to the host interior and can be easily displaced by more strongly binding guests. Since sandwich complexes were observed to be suitable guests, the encapsulation of more chemically reactive organometallic half-sandwich compounds was attempted.

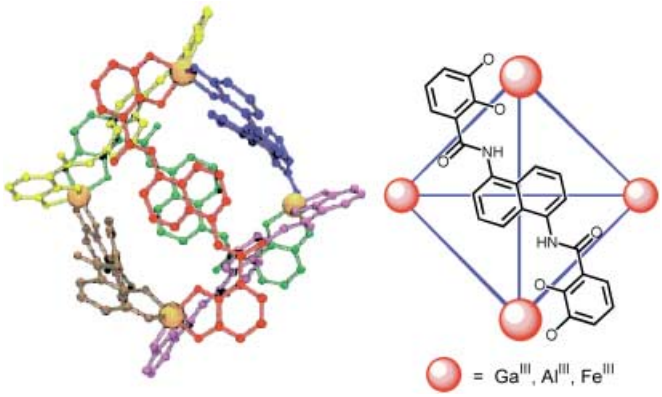

Figure 1. Left: view down the twofold axis of the crystal structure of the tetrahedral supramolecular $[M_4L_6]^{12-}$ host which can encapsulate monocationic guest molecules. Ligands are colored for differentiation. Right: schematic representation showing the structure of one of the six identical ligands that span the edges of the tetrahedral host.

In organic solvents, the half-sandwich complex [Cp*(PMe_3)Ir(Me)OTf] (**1**; Cp* = η^5-C_5Me_5, OTf = OSO_2CF_3 = triflate) thermally activates the C–H bonds of a wide range of organic molecules, including methane, at low temperatures. This process is believed to occur by dissociation of the anionic triflate ligand to form a reactive monocationic iridium intermediate $[Cp^*(PMe_3)Ir(Me)]^+$.[19–21] Therefore, we chose to explore the encapsulation of **1** with the intention that encapsulation of this species would allow for the observation of similar C–H bond-activation reactions with selectivity preferences controlled by the well-defined cavity of the host assembly.

However, upon addition of $[Na_4(NMe_4)_7][NMe_4{\subset}Ga_4L_6]$ to **1** in aqueous solution, no encapsulation was observed, presumably a result of the relatively high desolvation enthalpy of the hydrated species [Cp*(PMe_3)Ir(Me)(OH_2)][OTf]. The iridium methyl ethene adduct [Cp*(PMe_3)Ir(Me)(C_2H_4)][OTf][22] (**2**) was then targeted as a better guest candidate, since it was anticipated that the additional ethene

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ligand would increase π–π interactions with the host interior as well as increase the hydrophobicity of **2** owing to the absence of a coordinated solvent molecule.

In contrast to the lack of encapsulation of **1**, a mixture of racemic **2** and racemic $[Na_4(NMe_4)_7][NMe_4{\subset}Ga_4L_6]$ in aqueous solution led to displacement of the internal $[NMe_4]^+$ ion and immediate formation of the host–guest assembly $[Na_3(NMe_4)_8][Cp^*(PMe_3)Ir(Me)(C_2H_4){\subset}Ga_4L_6]$ (**3a**), as established by ^1H and ^{31}P NMR spectroscopy. Owing to the ring-current effect of the naphthalene backbone surrounding the host cavity, the NMR resonance signals for an encapsulated guest are shifted upfield, a useful diagnostic feature. The host–guest assembly is a mixture of two diastereomers owing to encapsulation of the chiral iridium guest within the chiral host assembly with only modest diastereoselectivity. Evidence for these diastereomers is seen in two sets of upfield-shifted resonance signals in ^1H and ^{31}P NMR spectra (Figure 2a).

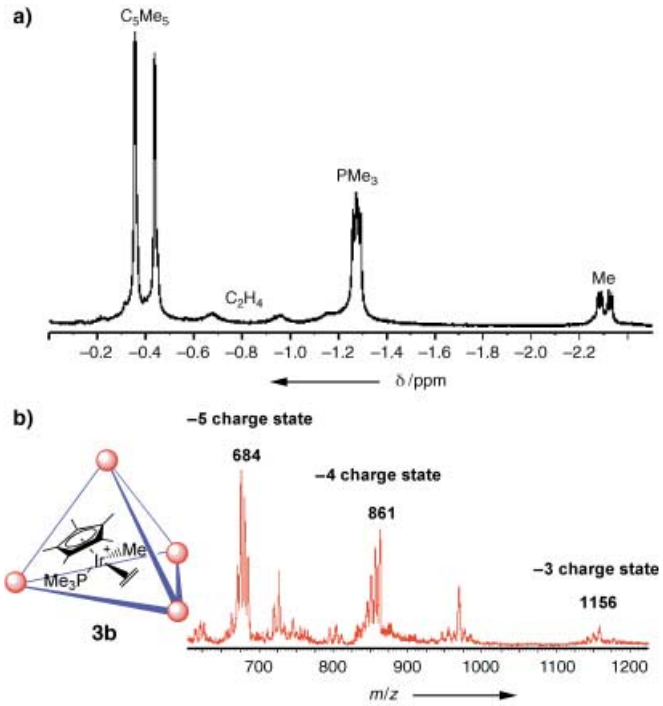


Figure 2. a) ^1H NMR spectrum of **3a** showing upfield resonances corresponding to the diastereomeric encapsulated guest molecule. b) Electrospray mass spectrum of **3b** displaying peaks corresponding to the intact host–guest complex with varying numbers of sodium counterions. Minor peaks correspond to the intact host–guest complex with a second equivalent of the iridium species associated with it, presumably coordinated to the exterior of the host assembly.

Notably, the peaks corresponding to the Cp* protons of the iridium complex are now shifted upfield from a single peak at $\delta = 1.96$ ppm for the unbound species to two signals at $\delta = -0.35$ and -0.44 ppm corresponding to the two diastereomeric host–guest assemblies. In the ^{31}P NMR spectrum, the resonance corresponding to the encapsulated iridium species has been shifted upfield from a single peak at $\delta = -29.1$ ppm to two diastereomeric signals at $\delta = -37.1$ and -37.9 ppm.

To reduce the number of counterions in solution and to remove the possible complications of $[NMe_4]^+$ guest competition, **2** was added to the formally "empty" $Na_{12}[Ga_4L_6]$ assembly (prepared in the absence of NMe_4Cl) to form $Na_{11}[Cp^*(PMe_3)Ir(Me)(C_2H_4){\subset}Ga_4L_6]$ (**3b**). Electrospray mass spectrometry data afforded signals of the intact host–guest assembly corresponding to the $\{Na_8[Cp^*(PMe_3)Ir(Me)(C_2H_4){\subset}Ga_4L_6]\}^{3-}$, $\{Na_7[Cp^*(PMe_3)Ir(Me)(C_2H_4){\subset}Ga_4L_6]\}^{4-}$, and $\{Na_6[Cp^*(PMe_3)Ir(Me)(C_2H_4){\subset}Ga_4L_6]\}^{5-}$ charge states at 1156 *m/z*, 861 *m/z*, and 684 *m/z*, respectively (Figure 2b). An MM2 molecular mechanics optimized structure of **3b** predicts that the iridium species will fit within the cavity of the host assembly with ample room for small substrates (Figure 3).[23]

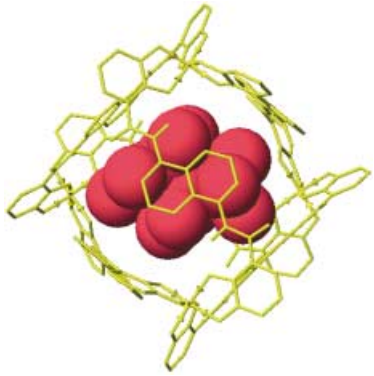
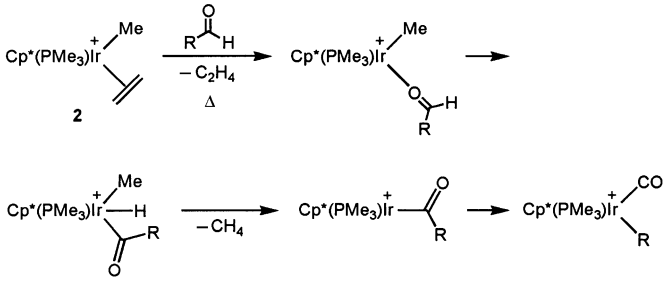


Figure 3. Molecular mechanics optimized structure of host–guest assembly **3b** containing encapsulated iridium species (red).

Despite ethene coordination, complex **2** (unencapsulated) remains reactive and undergoes C–H bond activation reactions with aldehydes (RCHO) in aqueous solution at 75 °C. Presumably, the ethene ligand is able to dissociate at this temperature, which allows the metal center to activate the aldehyde C–H bond and form an iridium acyl intermediate. This step is followed by migratory deinsertion of the carbonyl group to give a cationic iridium alkyl carbonyl product $[Cp^*(PMe_3)Ir(R)(CO)][OTf]$, analogous to the mechanism of activation of aldehydes by **1** (Scheme 1).[24]

When acetaldehyde (**4**) was added to an aqueous solution of iridium host–guest assembly **3b** and heated to 75 °C, a new encapsulated product was detected in moderate yield after



Scheme 1. Mechanism of C–H bond activation with aldehydes.

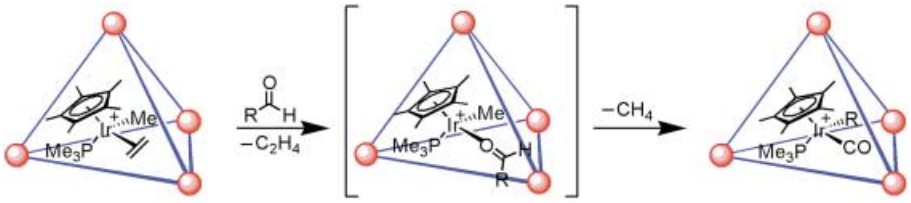
several days.[25] This guest species was identified as $[Cp^*(PMe_3)Ir(Me)(CO)]^+$, which results from the C–H bond activation of acetaldehyde by the supramolecular host–guest assembly (reaction illustrated at the top of Table 1). In addition to ^1H and ^{31}P NMR spectroscopy, and electrospray mass spectrometry data consistent with the formation of this product host–guest assembly, infrared spectroscopy revealed a sharp absorbance for a new metal carbonyl stretch $\tilde{\nu}_{CO}$ at 2022 cm^{-1}, which confirms the formation of an iridium carbonyl species. Furthermore, addition of independently prepared product iridium methyl carbonyl species to $Na_{12}[Ga_4L_6]$ at 75 °C yielded the spectroscopically identical host–guest assembly. Since the product iridium alkyl carbonyl guest is also chiral, the host assembly induces product formation with a diastereomeric ratio (d.r.) that can easily be detected by NMR spectroscopy. In this case, the diastereoselectivity is relatively small, 60:40.

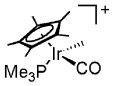
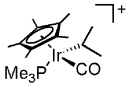
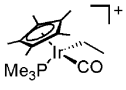
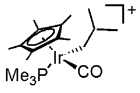
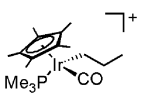
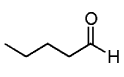
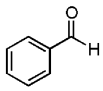
The selectivity in the encapsulated C–H bond-activation reactions was explored by examining a variety of aldehyde substrates (Table 1). The products were all characterized as above. These results display significant dependence on the size and shape of the aldehyde during diastereoselective product formation. As the size of straight-chain alkyl aldehyde substrates increased progressively from acetaldehyde (**4**) to propionaldehyde (**5**) and then to butyraldehyde (**6**), the d.r. also increased from 60:40 to 65:35 and then to 70:30. Presumably, the larger guests come into closer contact with the interior of the host assembly and the chirality of the host cavity is expressed more effectively. However, while substrates with sizes from acetaldehyde to butyraldehyde react with the host–guest assembly **3b**, *no reaction* occurred with larger aldehydes, such as valeraldehyde (**7**) and benzaldehyde (**8**). These aldehydes are apparently too large to enter the cavity of the host assembly and, as such, cannot interact with the encapsulated iridium complex. This result emphasizes the ability of the well-defined cavity of the host assembly to control the access of substrates to the reactive, but encapsulated, metal center. This selectivity is remarkably effective: even after weeks at elevated temperatures, the iridium methyl ethene guest does not "leak out" of the host and react with the substrate.

In addition to size selectivity, shape selectivity plays a key role in the encapsulated C–H bond-activation reactions. The host–guest assembly **3b** reacts with isobutyraldehyde (**9**) with a lower diastereomeric ratio than with butyraldehyde (d.r. of 55:45 vs. 70:30). We hypothesize that the iridium isobutyraldehyde intermediate has a more spherical shape than the butyraldehyde complexes, which results in decreased diastereoselective recognition by the host nanovessel. Valeraldehyde (**7**), isovaleraldehyde (**10**), 2-methylbutanal (**11**), and pivalaldehyde (**12**) are all five-carbon-skeleton structural isomers. However, only **10** reacts with the encapsulated iridium complex **3b**, with a d.r. of 58:42. Even after extended periods at elevated temperatures, the structural isomers **7**, **11**, and **12** do not react with the encapsulated metal center. It appears that, of this group of isomeric compounds, only **10** has the right shape to fit inside the host interior containing the reactive metal center.[26,27]

The above selectivity results require that the C–H bond activation of aldehydes must occur within the cavity of the host assembly rather than by dissociation from the capsule, reaction with aldehyde, and then re-entry into the nanovessel. This selectivity is markedly illustrated in two competition experiments. When 0.5 equivalents each of **4** and **8** were added at 75 °C to one equivalent of the unencapsulated iridium complex **2** in aqueous solution, two products corresponding to the methyl carbonyl and the phenyl carbonyl iridium complexes are formed in a 1:1 ratio. Thus, there is no selectivity in the reaction of the unbound complex with regard to the activation of these two aldehydes. However, when the same competition experiment was performed with the encapsulated iridium complex **3b**, only the methyl carbonyl guest product was detected upon heating to 75 °C. Compound **4** reacts quantitatively to form the 0.5 equivalents of encapsulated methyl carbonyl product, leaving 0.5 equivalents of host–guest assembly **3b** and 0.5 equivalents of **8**, thus demonstrating the ability of the host–guest complex

Table 1: Observed steric and diastereoselectivities in the C–H bond activation of aldehydes by the encapsulated iridium host–guest complex.



	Substrate	Guest product[a]	d.r.		Substrate	Guest product[a]	d.r.
4			60:40	**9**			55:45
5			65:35	**10**			58:42
6			70:30	**11**		n. r.	n/a
7		n. r.	n/a	**12**		n. r.	n/a
8		n. r.	n/a				

[a] n. r. = no reaction.

to selectively activate one substrate from a mixture of chemically very similar substrates in situ.

In conclusion, we have described the supramolecular encapsulation of reactive transition-metal complexes in a host nanovessel and the first case of C–H bond activation under such reaction conditions. The C–H bond activation of aldehydes proceeds with highly specific size and shape selectivity, as well as modest diastereoselectivity, in this new iridium host–guest assembly.

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Keywords: C–H activation · diastereoselectivity · gallium · host–guest systems · iridium · supramolecular chemistry

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[25] Yields ranging from 40–60% were obtained in these aldehyde activation reactions. At this temperature, some decomposition of the iridium metal complex to intractable products is observed for both the free and encapsulated species. Specific experimental yields are presented in the Supporting Information.
[26] This selectivity is due to differences in shape and size rather than hydrophobicity of the substrate. Both **10** and **12** have the same hydrophobicity value as determined by an octanol/water partition experiment, but only **10** is activated by the encapsulated iridium host–guest complex.
[27] CAChe MM2 force field molecular mechanics calculations could not detect a substantial difference in substrate binding selectivity. More sophisticated calculations have not yet been undertaken.

