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Unprecedented Encapsulation of Carbonyl Guest with Designer Lewis Acid Receptor**

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Physical inclusion of small molecules can be commonly effected with zeolites, cyclodextrins, and synthetic macrocycles as host molecules.[1–6] The self-assembly of cavity-forming smaller subunits serves as another strategy to encapsulate guest molecules.[7] We report here a new encapsulation of guest substrates with a bowl-shaped Lewis acid host, aluminum tris(2,6-diphenylphenoxide) (ATPH),[8] based on the Lewis acid – base complex formation. The resulting Lewis acid capsules persist over timescales that are sufficient to enable chemical processes to take place within them. Therefore, they serve a double function, as substrate protector and accelerator, in selective organic transformations (Figure 1).

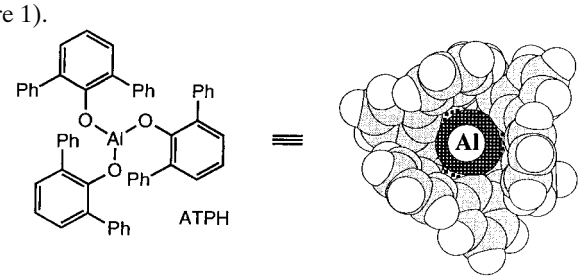

Figure 1. Space-filling model of aluminum tris(2,6-diphenylphenoxide) (ATPH) with an appropriate bowl-shaped cavity for guest molecules.

The Lewis acid receptor ATPH and its congeners self-assemble with a dicarbonyl guest molecule in organic solvents to form a dimeric capsule. The X-ray crystal structure of such a complex with 1,4-dimethylpiperazine-2,5-dione as a model guest is shown in Figure 2.[9, 10] Intermolecular coordinative

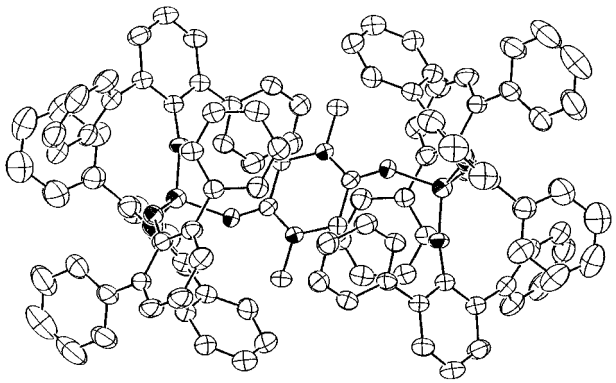

Figure 2. ORTEP diagram of the molecular capsule of ATPH and 1,4-dimethylpiperazine-2,5-dione through coordinative bonding. The solvent molecules (CH_2Cl_2) and all hydrogen atoms are omitted for clarity.

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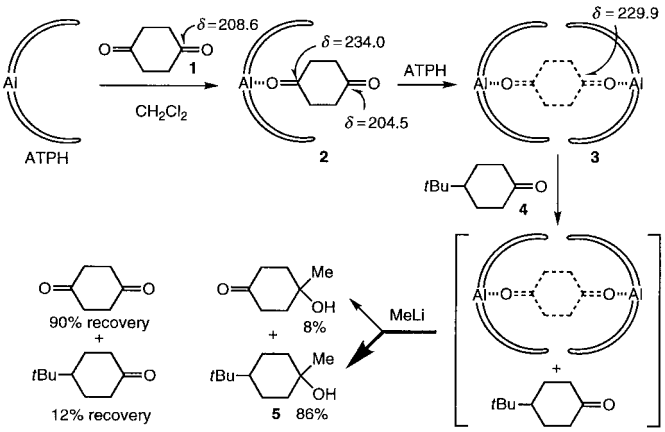
bonds between ATPH and carbonyl moiety hold the two subunits together. A similar capsule is formed with ATPH and 1,4-cyclohexanedione (**1**) (Scheme 1). In $CDCl_3$ the equilibrium shifts largely to the 2:1 ATPH complex **3**: ^{13}C NMR



Scheme 1. Stepwise encapsulation of 1,4-cyclohexanedione (**1**) with one and two equivalents of ATPH by complex formation through Lewis acid–base interactions, and its reaction with methyllithium in the presence of another carbonyl substrate.

measurements in $CDCl_3$ with 0.5 equivalents of ATPH and **1** at room temperature show the sharp and well-defined signals of the 1:1 ATPH/diketone complex **2** together with the peak of free **1** (Figure 3b). A considerable downfield shift is observed for the signal of the carbonyl group in **2** ($\delta = 234.0$; Figure 3b and c); and the signal for the uncomplexed carbonyl group appears at $\delta = 204.5$ (Figure 3b,c) which is shifted slightly upfield relative to that of the free 1,4-cyclohexanedione (**1**; $\delta = 208.6$, Figure 3a). After the addition of another

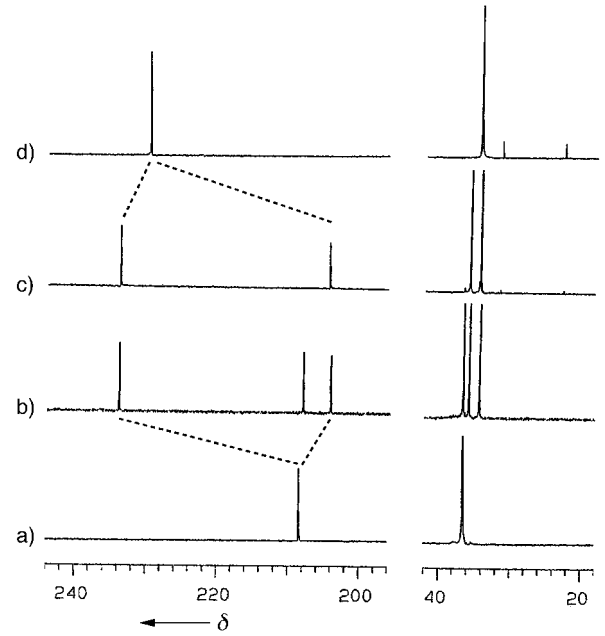
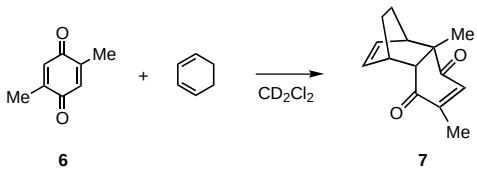


Figure 3. Signals of the carbonyl groups (left) and α-carbon atoms (right) in the ^{13}C NMR spectrum of 1,4-cyclohexanedione (**1**) and its complex with ATPH in $CDCl_3$. a) **1** alone; b) **1** with 0.5 equivalents of ATPH; c) **1** with one equivalent of ATPH; d) **1** with two equivalents of ATPH.

0.5 equivalents of ATPH, the carbonyl signal of free **1** completely disappeared (Figure 3c). Addition of one more equivalent of ATPH to this solution affords, under induction by the guest molecule **1**, the capsular form **3**, which is confirmed by the sharp single peak for the coordinated carbonyl group at $\delta = 229.9$ (Figure 3d). The capsule **3** was found to be stable in the presence of another carbonyl substrate. Indeed, addition of 4-*tert*-butylcyclohexanone (**4**) (1 equiv) to the dimeric complex **3** at $-78\,^{\circ}C$ and subsequent treatment with MeLi (1 equiv) at $-78\,^{\circ}C$ resulted in predominant formation of 4-*tert*-butyl-1-methylcyclohexanol (**5**) (86%) with 90% recovery of the diketone **1**.[11]

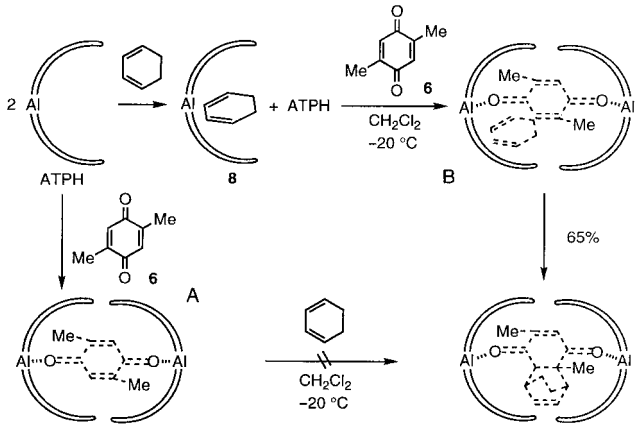
Simple addition of MeLi (1 equiv) to an equimolar mixture of **1** and **4** at $-78\,^{\circ}C$ gave 4-hydroxy-4-methylcyclohexanone and **5** in 49% and 47% yields, respectively. These results suggest the promising encapsulation of the diketone **1** in the presence of another carbonyl substrate, and two equivalents of ATPH can be utilized as an effective protector for the dicarbonyl compound **1** in the alkylation even with highly reactive organolithium nucleophiles.

With this information at hand, we studied the Diels–Alder reaction between 2,5-dimethyl-*p*-benzoquinone (**6**) and cyclohexa-1,3-diene. This cycloaddition proceeds very slowly at room temperature. In CD_2Cl_2 at molar concentrations of each component, no cycloadducts are detected by NMR spectroscopy after about two days [Eq. (1)]. Initial addition of 2,5-dimethyl-*p*-benzoquinone (**6**) (1 equiv) to ATPH (2.2 equiv)



(1)

in CH_2Cl_2 at $-20\,^{\circ}C$ and subsequent treatment with cyclohexa-1,3-diene (1.1 equiv) resulted in only traces of the *endo*-cycloadduct **7**. This is due to the virtually complete protection against diene approach by the efficient encapsulation of quinone substrate (route A in Scheme 2).[11] In marked



Scheme 2. Encapsulation of 2,5-dimethyl-*p*-benzoquinone (**6**) and cyclohexa-1,3-diene with two equivalents of ATPH accelerates the Diels–Alder reaction. Cyclohexa-1,3-diene is selectively included by electronic interaction of the diene portion with the concave aromatic interior of ATPH.

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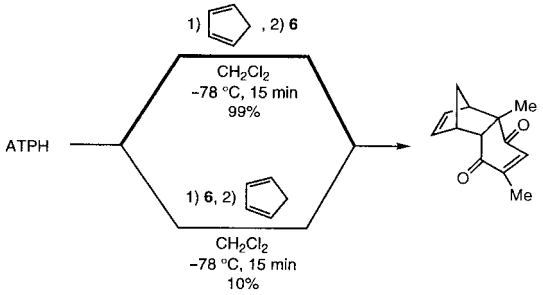
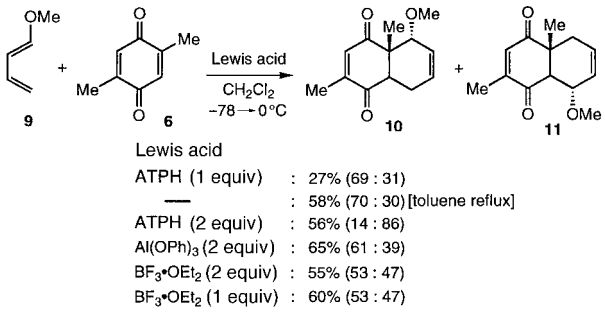
contrast, however, mixing of cyclohexa-1,3-diene (1.1 equiv) and ATPH (2.2 equiv) in CH_2Cl_2 at $-20\,^{\circ}C$ and subsequent addition of 2,5-dimethyl-*p*-benzoquinone (**6**) (1 equiv) under similar reaction conditions afforded the *endo*-cycloadduct **7** in 65% yield (route B in Scheme 2). This observation implies the effective inclusion of diene component by electronic interactions of the diene portion with the concave aromatic interior of the cavity of ATPH (**8** in Scheme 2). This facilitates the smooth cycloaddition on complexation and the capsule formation with a quinone substrate **6**.[12] A similar tendency is observed in the Diels–Alder reaction between 2,5-dimethyl-*p*-benzoquinone (**6**) and cyclopentadiene (Scheme 3).



Scheme 3. Rate acceleration of the Diels–Alder reaction of 2,5-dimethyl-*p*-benzoquinone (**6**) and cyclopentadiene by encapsulation.

In CD_2Cl_2, the Diels–Alder adduct **7** is readily encapsulated by ATPH, and a ^{13}C NMR signal unique to the encapsulated species can be observed. The original signals of the two carbonyl groups of the free compound **7** appeared at $\delta = 200.68$ and $\delta = 203.12$. Upon treatment with two equivalents of ATPH in CD_2Cl_2 at room temperature, these two signals significantly shifted downfield to $\delta = 211.56$ and $\delta = 216.38$, respectively, which supports the idea that the Diels–Alder adduct **7** is also a welcome guest. Therefore, the product can remain inside the capsule after the cycloaddition.

Another interesting feature of the present molecular assembly is the regio- and stereoselective Diels–Alder reactions of quinones and heterodienes that are capable of coordinating. The cycloaddition of quinone **6** with 1-methoxy-1,3-butadiene (**9**) (1 equiv) in the presence of ATPH (1 equiv) in CH_2Cl_2 at $-78 \rightarrow 0\,^{\circ}C$ for 1 h proceeded with complete *endo* preference to furnish the cycloadducts **10** and **11** in 27% combined yield in a ratio of 69:31 (Scheme 4); this result was



Scheme 4. Regioselective Diels–Alder reaction of **6** with methoxy diene **9** by means of the molecular assembly.

comparable with that of the thermal reaction in refluxing toluene for 15 h (58% yield; **10**:**11** = 70:30).[11] However, initial treatment of **9** with two equivalents of ATPH and subsequent addition of **6** (1 equiv) under similar reaction conditions afforded the cycloadducts **10** and **11** in 56% yield, and the regioselectivity was totally reversed (**10**:**11** = 14:86). This indicates that the preorganization of the heterodiene **9** and quinone **6** by complexation with ATPH prior to the capsule formation plays a crucial role in obtaining otherwise unattainable regioselectivity. The unusual regiochemical preference was lost when the cycloaddition was promoted by aluminum triphenoxide (2 equiv); commonly used Lewis acids such as $BF_3 \cdot OEt_2$ resulted in a total lack of selectivity regardless of the stoichiometry.

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[9] Crystal data: $C_{116}H_{92}Al_2N_2O_8Cl_4$, $M_W = 1797.44$, monoclinic, space group $P2_1/n$, $T = 298$ K, $a = 16.897(4)$, $b = 14.626(3)$, $c = 19.586(4)$ Å, $\beta = 94.41(1)^{\circ}$, $V = 4826.0(1)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.237$ g cm^{-1}, 3169 reflections obtained, $R = 0.065$, $R_w = 0.063$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-103289. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
[10] Although the relative binding strengths of the guests studied here have not been established precisely, it may be predicted based on our previous observation on the binding priority of various oxygen-containing substrates with a Lewis acidic bulky organoaluminum reagent (K. Maruoka, S. Nagahara, H. Yamamoto, *Tetrahedron Lett.* **1990**, *31*, 5475.)
[11] The concentration of the substrate was 0.0625 M in each case.
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