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Selective catalytic hydration of alkynes using Au-cavitands: a study in structure-activity relationship

Mami Inoue,[a] Katto Ugawa, Tomoyuki Maruyama, and Tetsuo Iwasawa*[a]

Abstract: The effect of catalytic cavity of a gold functionalized cavitand has been studied in the hydration reaction of internal alkynes. Variations on cavitand structures reveal the importance of two features that were studied: 1) flanking aromatic rings and 2) an adjacent P=O moiety. The di-quinoxaline-spanned resorcin[4]arene provides a well-defined compartment, where a cationic Au activates an internal alkyne for conversion to a ketone by delivery of water that has also been activated, this time by a P=O moiety. We synthesized four variations on our parent cavitand. Variations of the walls include replacement of quinoxalines with pyrazines or methylenes. Variation of the P=O center was accomplished with methylene or quinoxaline. All variants resulted in lower catalytic activity or selectivity, allowing us to confirm the significance of both an internal cavity and an activation site for water.

Introduction

Cram *et al* suggested in 1982 that the class name *cavitand* is synthetic organic compounds that contain *enforced cavities* large enough to accommodate simple molecules or ions.[1] Since the important classification, cavitand research has taken many paths. One of these paths leads to the emergence of catalyst centers being placed around or inside the enclosed space. The resemblance to enzymes is significant because the presence of a confined space and active site are present in both classes of supramolecules.[2, 3] Four classes of platforms (calixarenes,[4] cyclotriveratrylenes,[5] cyclodextrins,[6] and resorcinarenes[7]) have received attention. Particularly, the preparation of cavitands containing reactive metal centers, and their deployment for catalytic use are relevant to this report.

Thus far, there are not many successful reports of examples of catalytic cavitands. Embedding metal centers with introverted orientation presents several synthetic challenges.[8] Consequently, knowledgement is limited as to how these supramolecular chemistries contain features and principles that will be significant to the advancement of chemical catalysis.

We recently synthesized a cavitand of di-quinoxaline-spanned resorcin[4]arene **1**•AuCl that directs P-Au and P=O inwardly (Figure 1(a)), and found it efficiently catalyzes regio-selective hydration of unsymmetrical internal alkynes such as simple 3-octyne and 1-phenyl-1-butyne.[9] Our working hypothesis consisted of three main points as depicted in Figure 1(b): 1) the cationic Au atom activates the triple bond,[10] 2) Lewis basic P=O forms a hydrogen bonding with a water molecule,[11] 3) side-chain recognition is based on length and selective fit. Our initial report led us to the desire to uncover a more detailed structure-activity relationship. Our hypotheses were supported by our initial screening with **1**•AuCl: for example, 3-octyne is hydrated at the 3-position to yield 3-octanone in 91% yield, not 4-octanone.[9] We speculated that the π-surface of two quinoxaline walls plays a role in either recognition or stabilization of intermediates. Previously these walls played an essential role in alkyne-alkyne cross-coupling with two facing Au-centers.[12] The role of the P=O group also should be clarified. These can be tested with new cavitand variations. To facilitate this study, we found that preparation of our desired variants was possible with the more robust P-OCH_3 that also supports gold. Thus, **2**•AuCl is the starting point for this study, as opposed to our initial catalyst with P-$N(CH_3)_2$ (**1**•AuCl) (Figure 1(a)).

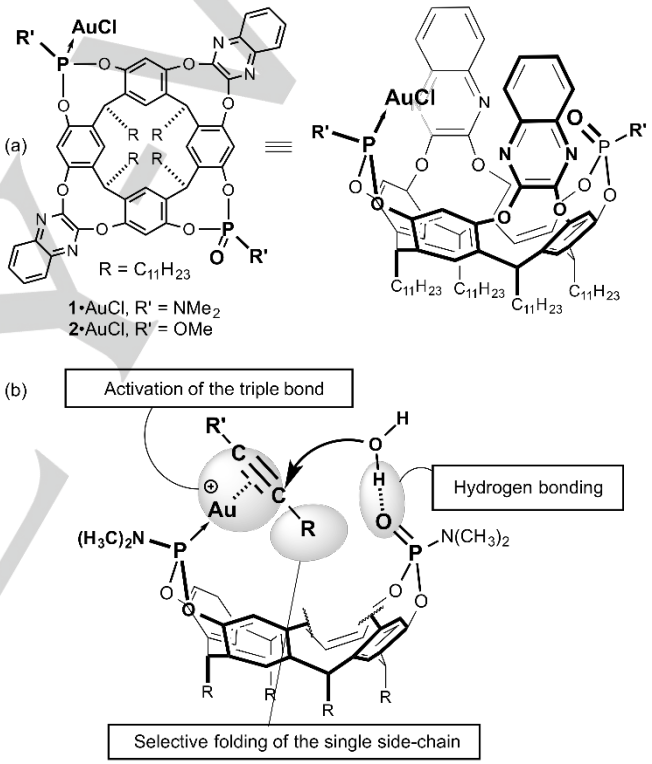

Figure 1. (a) Mono-AuCl cavitands **1**•AuCl and **2**•AuCl, and (b) working hypothesis of three points: (1) coordination of Au^+ toward an alkyne triple bond; (2) hydrogen bonding between P=O and H_2O; (3) selective folding of single side-chain (the two quinoxaline walls are omitted for ease of viewing).

Herein we report the synthesis of **2**•AuCl and corresponding variants **3**•AuCl, **4**•AuCl, **5**•AuCl, and **6**•AuCl (Figure 2). We include a direct comparison of their catalytic capabilities in chemical transformations illustrated in Scheme 1. **3**•AuCl and **4**•AuCl are variations where we have replaced P=O group of **2** with methylene or quinoxaline substructure. The **5**•AuCl shrinks the hight of the walls, now two pyrazines exist in the place of quinoxalines. **6**•AuCl removes the walls completely. We anticipated that comparative experiments test the hypothesis of Figure 1(b) as well as enhance the value of skeletal structure of **2** in chemical catalysis.[13]

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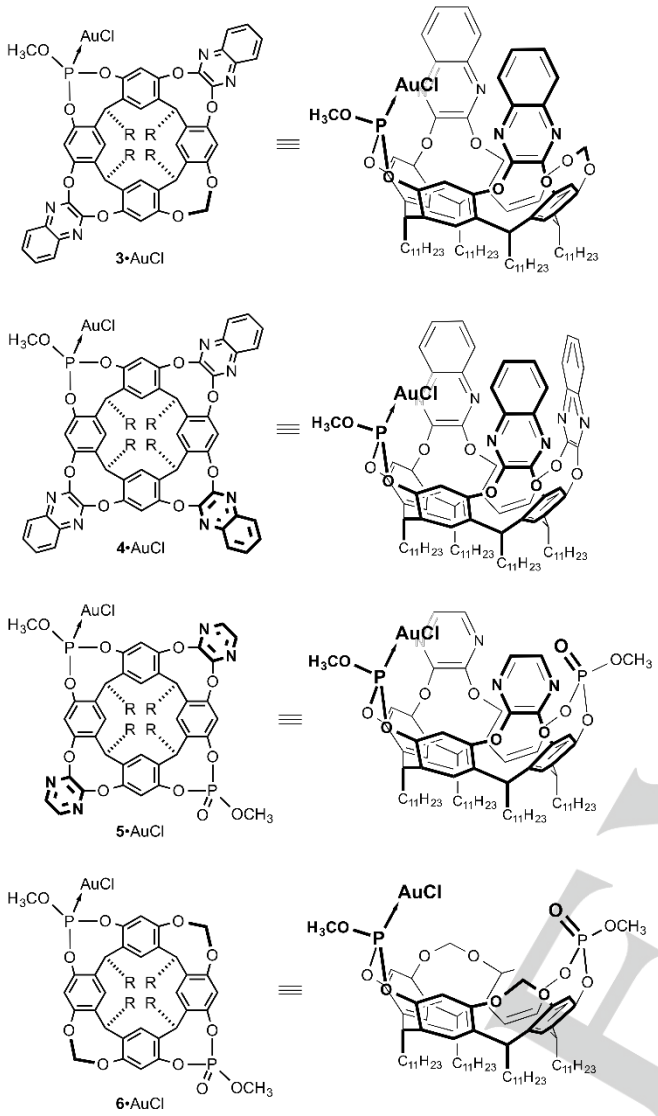
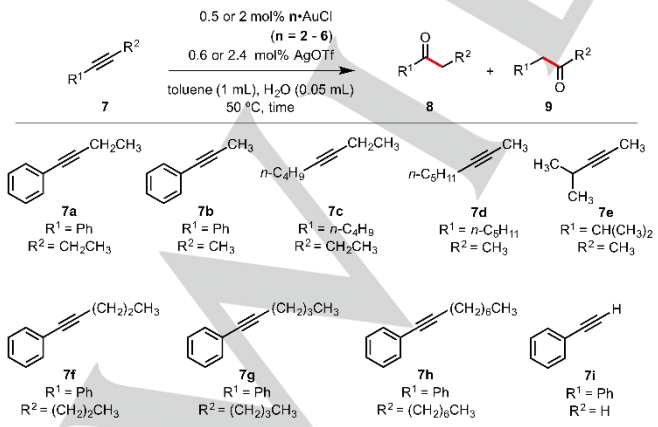


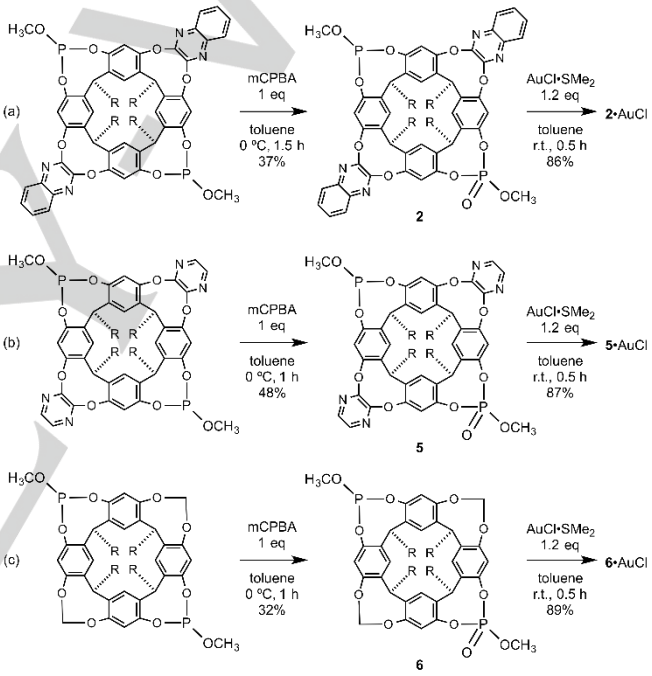
Figure 2. The model compounds of **3**•AuCl, **4**•AuCl, **5**•AuCl, and **6**•AuCl (R = $C_{11}H_{23}$).



Scheme 1. Au-catalyzed regio-selective hydration reactions of internal alkynes **7a**-**i** to produce isomeric ketones **8a**-**i** and **9a**-**i**.

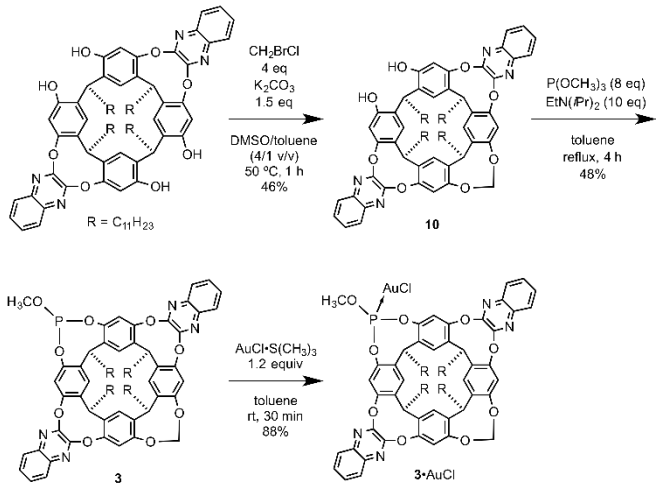
Results and Discussion

We started to synthesize new cavitands **2**•AuCl, **5**•AuCl, and **6**•AuCl as depicted in Scheme 2. The mCPBA-mediated *mono*-oxidation of the corresponding bis-phosphite compounds yielded **2** in 37%, **5** in 48%, and **6** in 32%.[9] The following complexation with AuCl•$S(CH_3)_2$ smoothly occurred, forming **2**•AuCl, **5**•AuCl, and **6**•AuCl in 86%, 87%, and 89% yields, respectively.



Scheme 2. Synthesis of (a) **2** and **2**•AuCl, (b) **5** and **5**•AuCl, and (c) **6** and **6**•AuCl.

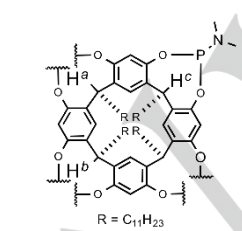
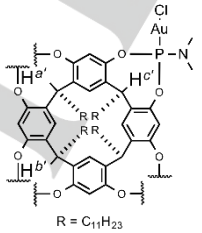
For synthesis of **3**•AuCl, the three steps route was illustrated in Scheme 3: first, the tetra-ol platform reacted with CH_2BrCl to form **10** in 46% yield. Then, reaction of $P(OCH_3)_3$ with **10** gave two isomeric compounds in which the desired **3** (48%) orients $POCH_3$ moiety outwardly (*iso*-**3**, 13% yield inwardly). The chemical shift of **3**'s $POC\underline{H}_3$ by ^{1}H NMR spectroscopy is located at 3.97 ppm for **3** and 3.22 ppm for *iso*-**3**. The anisotropic effect by the internal π-cloud shifts the inside $OC\underline{H}_3$ of *iso*-**3** toward up-field region as compared with that of **3**. The clean complexation between **3** and AuCl•$S(CH_3)_2$ proceeded in 88% yield. We previously reported the synthesis of **4**•AuCl[14]



Scheme 3. Synthesis of **3** and **3**•AuCl.

We made the following observations about the solution dynamics of **2** - **6** and **2**•AuCl - **6**•AuCl. 4-Walled quinoxaline cavitands are known to fluctuate between vase (closed) and kite (open) conformations, and reports on the effects of solvent and acid are known.[15] Typically, methine protons around 5.5 ppm are indicative of vase conformers, whereas 3.7 ppm indicates the kite form. For **2** and **2**•AuCl in Table 1, protons H^b and H^c are in a different electronic environment than the other proton H^a: H^a in [D_8]toluene solvent clearly demonstrates the vase is preferred. For **3**, we see nearly identical behavior of the methines when comparing to the parent **2**. For **4**, protons H^a and H^b are consistent with a vase shape. For **5** and **6**, no major perturbations to structure from a vase shape are observed. Thus, cavitands are in vase-like conformations and the Au metal centers are pointing inwardly while dissolved in toluene. This is consistent with our previous work which includes solid state single crystal X-ray data.[12, 14]

Table 1. NMR chemical shifts of the methine protons H^a - H^c for **n** and **n**•AuCl. [a]

n	 **n** (**n** = 2 ~ 6)			 **n**•AuCl		
	H^a	H^b	H^c	$H^{a'}$	$H^{b'}$	$H^{c'}$
2	6.04	4.97	5.03	6.02	4.72	4.91
3	6.14	4.88	5.02	6.14	4.63	4.93
4	6.05	4.91	6.11	6.03	4.65	6.07
5	5.98	4.92	5.02	6.02	4.60	4.85
6	4.93	5.02	4.93	5.02	4.84	4.57

[a] 5 mg samples in 0.5 mL of [D_8]toluene, 400 MHz.

With a collection of new cavitands prepared, we evaluated the differences in reactivities between **2**, **3** and **4** with the hydration of alkynes **7a**-**e** as planned *via* Scheme 1. The results of these experiments are summarized in Table 2, which revealed the role of the P=O substructure of **2**. For entry 1, **2** gave **9a** in 88%, a minor isomer **8a** in 2% yield. For entries 2 and 3, **3** didn't catalyze the hydration even in the presence of external O=PPh_3. Prolonged reaction time (entry 4) ultimately gave 71% of **9a** and 12% of **8a**. For entries 5-7, three-walled **4** resulted in up to 38% yield of **9a** only after prolonged overnight reaction with external O=PPh_3. For entries 8-10 in which alkyne **7b** was used, the results with **2** versus **3** and **4** were more pronounced. This trend continued in alkyne **7c** (entries 11-13), **7d** (entries 14-16) and **7e** (entries 17-19). Even though the hydration occurred in the presence of **3** and **4**, the ketone distribution of **8** to **9** were never better than with **2**. Thus, the covalently appended P=O group as seen in **2** is essential for efficient and selective hydration.

Table 2. Evaluation of reactivities of **2**•AuCl, **3**•AuCl, and **4**•AuCl conducted *via* Scheme 1. [a]

Entry	Alkyne	mol% of **n**•AuCl	**n**	mol% of O=PPh_3	*t* [h]	Yield[b][c] [%]		
						7	**8**	**9**
1	**7a**	0.5	**2**	-	1	0	2	88
2			**3**	-	1	100	0	0
3				0.5	1	71	<1	1
4				0.5	14	14	12	71
5			**4**	-	1	89	2	1
6				0.5	1	82	2	1
7				0.5	14	43	7	38
8	**7b**	0.5	**2**	-	1	0	1	99
9			**3**	0.5	1	>99	<1	0
10			**4**	0.5	1	99	<1	0
11	**7c**	2	**2**	-	1	0	9	91
12			**3**	2	1	36	33	31
13			**4**	2	1	3	47	50

14	**7d**	0.5	**2**	-	1	0	12	88
15			**3**	0.5	1	95	2	3
16			**4**	0.5	1	95	1	4
17	**7e**	2	**2**	-	1	0	17	83
18			**3**	2	1	30	21	49
19			**4**	2	1	10	27	63

[a] Conditions: toluene for **7a** and **7b**, and [D_8]toluene for **7c**-**e** (1 mL), H_2O (0.05 mL, 2.5 mmol), Au catalyst (0.01 mmol, 17 mg for **2**•AuCl, 17 mg for **3**•AuCl, 18 mg for **4**•AuCl), alkyne (appropriate amount for each entry), $O=PPh_3$ (appropriate amount for each entry). [b] Determined by ^{1}H NMR analyses on the basis of samples those were purified by short-plugged silica-gel column chromatography (eluent: toluene for **7a** and **7b**, [D_8]toluene for **7c**-**e**). ^{1}H NMR spectra of **8a**-**e** and **9a**-**e** were identical to those of commercially available authentic samples. [c] Unreacted **7**.

Next, we studied the influence of quinoxaline walls in **2.** Evaluation of the differences of reactivities between **2**, **5**, and **6** was carried out through the hydration reactions of **7a**-**i**, and selected results were summarized in Table 3.[16] For **2**•AuCl, **7b** and **7a** were selectively transformed into the corresponding ketones **9b** and **9a**, respectively (entries 1 and 2). The reactivity of **5**•AuCl showed a similar tendency toward that of **2**•AuCl, in which **7b** and **7a** undertook selective hydration reactions (entries 4-5). On the other hand, non-walled **6**•AuCl showed a kind of different reactivity: only **7a** was subjected to a selective reaction, and other substrates were almost unhydrated (entries 7-9). Noteworthy is that existences of pyrazine and quinoxaline walls allow **7b** to undertake hydration reactions (entries 2 and 5). These results indicate that all walls enhance the reactivity and selectivity.

Table 3. Evaluation of reactivities of **2**•AuCl, **5**•AuCl, **6**•AuCl conducted *via* Scheme 1 (R^1=Ph, 2 mol% Au catalyst). [a]

Entry	**n**	R^2	alkyne	Yield[b][c] [%]		
				7	**8**	**9**
1	**2**	CH_3	**7b**	0	1	99
2		CH_2CH_3	**7a**	0	3	90
3		$(CH_2)_2CH_3$	**7f**	81	6	13
4	**5**	CH_3	**7b**	0	11	89
5		CH_2CH_3	**7a**	0	3	86
6		$(CH_2)_2CH_3$	**7f**	41	19	40
7	**6**	CH_3	**7b**	95	3	2
8		CH_2CH_3	**7a**	<1	1	90
9		$(CH_2)_2CH_3$	**7f**	98	1	1

[a] Conditions: alkyne (0.5 mmol), toluene (1 mL), H_2O (0.05 mL, 2.5 mmol), Au catalyst (0.01 mmol, 17 mg for **2**•AuCl, 16 mg for **5**•AuCl, 15 mg for **6**•AuCl). [b] Determined by ^{1}H NMR analyses on the basis of samples those were purified by short-plugged silica-gel column chromatography (eluent: [D_8]toluene). [c] Unreacted **7**.

Conclusions

In conclusion, we probed the catalytic capability of **2**•AuCl in the selective hydrations of alkynes through structure-activity relationship by preparing four kinds of cavitands: **3**, **4**, **5**, and **6**. Comparative study using these model catalysts strongly suggests two salient features: One, a covalently attached P=O to the resorcin[4]arene core remarkably facilitates the water molecule to add the alkyne triple bond. This proximity effect was clearly shown in experiments where it was removed. Two, the π-cloud created by two flanking quinoxaline (or pyrazine) walls also plays a major role. This effect is most likely a result of stabilization of reactive intermediates and chemical processes.[17, 18, 19] This is a consequence to such a limited space of **2**, because this space would govern the shape of transition state. These results illustrate that the quinoxaline-spanned resorcin[4]arene skeleton can specifically designed to elicit selective catalysis. Previously this level of control using a supramolecular architecture had not been achieved to our knowledge. Further development of new catalytic cavitands is ongoing.

Experimental Section

General Methods: All reactions sensitive to air or moisture were carried out under an argon or a nitrogen atmosphere and anhydrous conditions unless otherwise noted. Dry solvents were purchased and used without further purification and dehydration. All reagents were purchased and used without further purification. Analytical thin layer chromatography was carried out on Merck silica $60F_{254}$. Column chromatography was carried out with silica gel 60 $_N$ (Kanto Chemical Co.). LRMS and HRMS were reported on the basis of TOF (time of flight)-MS (MADI-TOF or LCMS-IT-TOF), and DART (Direct Analysis in Real Time)-MS. ^{1}H and ^{13}C NMR spectra were recorded with a 5 mm QNP probe at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in d (ppm) with reference to residual solvent signals [^{1}H NMR: $CHCl_3$ (7.26), C_7H_8 (2.08), C_6H_6 (7.16), CH_2Cl_2 (5.32); ^{13}C NMR: $CDCl_3$ (77.0)]. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Synthesis of 2: (Scheme 2). To the parent bis-phosphite (296 mg, 0.2 mmol) in toluene (8 mL) at 0 ºC was slowly added a cooled-toluene solution of *meta*-chloroperbenzoic acid (mCPBA, 75%, 46 mg, 0.2 mmol) over 3 min. After stirred at 0 ºC for 1.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (4 mL), and stirred at ambient temperature for 40 min. The mixture was transferred into a 100 mL separatory funnel,

washed with water (20 mL) and brine (20 mL), and dried over Na_2SO_4, and concentrated *in vacuo* to give a crude of 285 mg as a white solid material. Purification by short-plugged column chromatography (SiO_2, toluene/EtOAc = 9/1) yield 112 mg of **2** in 37% as white solid powders. For data of **2**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.84-7.81 (m, 4H), 7.54-7.51 (m, 4H), 7.47 (s, 2H), 7.40 (s, 2H), 7.24 (s, 2H), 7.17 (s, 2H), 5.74 (t, *J* = 8.2 Hz, 2H), 4.59-4.55 (m, 2H), 4.09 (d, $^3J_{PH}$ = 11.4 Hz, 3H), 3.94 (d, $^3J_{PH}$ = 8.8 Hz, 3H), 2.36-2.20 (m, 8H), 1.45-1.28 (m, 72H), 0.91-0.87 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 153.0, 152.9, 152.8 (d, J_{CP} = 1.4 Hz), 152.6, 148.0 (d, J_{CP} = 5.0 Hz), 146.2 (d, J_{CP} = 6.7 Hz), 140.13, 140.09, 137.3, 137.2, 134.7, 134.1 (d, J_{CP} = 3.8 Hz), 129.8, 129.7, 128.5, 128.3, 123.3, 122.8, 118.0, 117.1, 56.1 (d, J_{CP} = 6.2 Hz), 50.2 (d, J_{CP} = 2.1 Hz), 36.2, 36.1, 34.3, 32.3 (many peaks are overlapped), 31.9, 31.6, 30.1 (many peaks are overlapped), 29.7 (many peaks are overlapped), 28.33, 28.28, 23.0 (many peaks are overlapped), 14.5 (many peaks are overlapped) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) 127.3, -13.5 ppm; MS (DART-TOF) *m/z*: 1494 $[MH]^+$; IR (neat): 2917, 2849, 1479, 1399, 1328, 1025 cm^{-1}; HRMS (DART-TOF) calcd for $C_{90}H_{119}N_4O_{11}P_2$: 1493.8345 $[MH]^+$, Found : 1493.8427; Anal. Calcd for $C_{90}H_{118}N_4O_{11}P_2$: C, 72.36; H, 7.96; N, 3.75. Found: C, 72.35; H, 7.87; N, 3.78.

Synthesis of 5: (Scheme 2). Under an argon atmosphere, to a solution of the parent bis-phosphite (174 mg, 0.13 mmol) in toluene (5.2 mL) at 0 ºC was slowly added a cooled-toluene solution of mCPBA (75%, 30 mg, 0.13 mmol). After stirred at 0 ºC for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (2.6 mL), and stirred at ambient temperature for 45 min. The mixture was transferred into a separatory funnel, and washed with water (10 mL) and brine (10 mL), and dried over Na_2SO_4, and concentrated *in vacuo* to give a crude of 167 mg as a white solid material. Purification by silica-gel column chromatography (toluene/EtOAc = 2/1) yielded **5** of 86 mg in 48% as white powders. For data of **5**: ^{1}H NMR (400 MHz, $CDCl_3$) 8.03 (d, *J* = 2.6 Hz, 2H), 8.01 (d, *J* = 2.6 Hz, 2H), 7.32 (s, 2H), 7.26 (s, 2H), 7.24 (s, 2H), 7.17 (s, 2H), 5.72 (t, *J* = 8.2 Hz, 2H), 4.57-4.54 (m, 2H), 4.07 (d, $^3J_{PH}$ = 11.4 Hz, 3H), 3.91 (d, $^3J_{PH}$ = 9.0 Hz, 3H), 2.28-2.18 (m, 8H), 1.14-1.27 (m, 72H), 0.91-0.87 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 154.7, 154.5, 153.1 (d, J_{CP} = 1.7 Hz), 152.9, 148.0 (d, J_{CP} = 5.2 Hz), 146.2 (d, J_{CP} = 6.7 Hz), 140.4, 140.2, 137.4 (d, J_{CP} = 2.6 Hz), 137.3 (d, J_{CP} = 2.2 Hz), 134.8, 134.1 (d, J_{CP} = 3.6 Hz), 123.5, 123.0, 117.9 (d, J_{CP} = 2.4 Hz), 117.1 (d, J_{CP} = 3.6 Hz), 56.1 (d, J_{CP} = 6.0 Hz), 50.3 (d, J_{CP} = 1.4 Hz), 36.2, 36.1, 34.1, 32.3 (many peaks are overlapped), 32.0, 31.7, 30.1 (many peaks are overlapped), 29.8 (many peaks are overlapped), 28.30, 28.29, 28.2, 23.0 (many peaks are overlapped), 14.5 (many peaks are overlapped) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) 128.0, -13.5 ppm; MS (MALDI-TOF) *m/z*: 1394 $[MH]^+$; IR (neat): 2925, 2853, 1479, 1395, 1296, 1137, 1029 cm^{-1}; HRMS (MALDI-TOF) calcd for $C_{82}H_{115}N_4O_{11}P_2$: 1393.8032 $[MH]^+$, Found : 1393.8079.

Synthesis of 6: (Scheme 2). Under an argon atmosphere, to a solution of the parent bis-phosphite (592 mg, 0.47 mmol) in toluene (18.8 mL) at 0 ºC was slowly added cooled-toluene solution of mCPBA (75%, 198 mg, 047 mmol). The reaction was quenched with saturated aqueous $NaHCO_3$ (9.4 mL), and stirred at ambient temperature for 35 min. The mixture was transferred into a separatory funnel, and washed with water (10 mL) and brine (10 mL), and dried over Na_2SO_4, and concentrated *in vacuo* to give a crude of 594 mg as a white solid material. Purification by silica-gel column chromatography (toluene/EtOAc = 4/1) yielded 192 mg of **6** in 32% as white powders. For data of **6**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.13 (s, 2H), 7.09 (s, 2H), 6.65 (s, 2H), 6.60 (s, 2H), 5.66 (d, *J* = 7.3 Hz, 2H), 4.74 (t, *J* = 8.1 Hz, 2H), 4.66 (d, *J* = 7.3 Hz, 2H), 4.60-4.55 (m, 2H), 4.05 (d, $^3J_{PH}$ = 11.4 Hz, 3H), 3.90 (d, $^3J_{PH}$ = 9.1 Hz, 3H), 2.23-2.18 (m, 8H), 1.42-1.27 (m, 72H), 0.90-0.87 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 155.7 (d, J_{CP} = 1.4 Hz), 155.4, 147.3 (d, J_{CP} = 4.8 Hz), 145.6 (d, J_{CP} = 7.4 Hz), 139.8 , 137.5 , 137.2, 134.1 (d, J_{CP} = 3.8 Hz), 121.7, 121.2, 117.7, 116.7 (d, J_{CP} = 4.1 Hz), 99.4, 56.0 (d, J_{CP} = 6.0 Hz), 50.2, 36.5, 36.1, 35.9, 32.3, 31.5, 30.9 , 30.3, 30.1, (many peaks are overlapped), 30.0 (many peaks are overlapped), 29.7, 28.23, 28.19, 23.0 (many peaks are overlapped), 14.4 (many peaks are overlapped) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) 127.3, -13.5ppm; MS (DART-TOF) *m/z*: 1283 $[M+NH_4]^+$; IR (neat): 2917, 2849, 1487, 1451, 1308, 1281, 1034, 961 cm^{-1}; HRMS (DART-TOF) calcd for $C_{76}H_{118}NO_{11}P_2$: 1282.8175 $[M+NH_4]^+$, Found : 1282.8215.

Synthesis of 2•AuCl: (Scheme 2). Under an argon atmosphere, to a 10 mL one-neck round-bottomed flask charged with a solution of **2** (75 mg, 0.05 mmol) in toluene (0.5 mL) was added AuCl•$S(CH_3)_2$ (18 mg, 0.06 mmol). After stirred at room temperature for 30 min, the reaction mixture was concentrated *in vacuo* to give a crude product. The crude was purified by short-plugged column chromatography (20 mL of hexane/EtOAc 2/1) to yield **2**•AuCl of 75 mg in 86% as white solid materials. For data of **2**•AuCl: ^{1}H NMR (400 MHz, $CDCl_3$) 7.93 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.83 (dd, *J* = 7.7, 2.0 Hz, 2H), 7.58-7.51 (m, 6H), 7.43 (s, 2H), 7.22 (s, 4H), 5.78 (t, *J* = 8.1 Hz, 2H), 4.59 (t, *J* = 7.9 Hz, 1H), 4.51 (t, *J* = 8.0 Hz, 1H), 4.13 (d, $^3J_{PH}$ = 13.9 Hz, 3H), 4.09 (d, $^3J_{PH}$ = 11.4 Hz, 3H), 2.31-2.25 (m, 8H), 1.45-1.27 (m, 72H), 0.92-0.86 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 153.1 (d, J_{CP} = 1.7 Hz), 152.9 (d, J_{CP} = 1.7 Hz), 152.34, 152.30, 146.3 (d, J_{CP} = 6.9 Hz), 144.5 (d, J_{CP} = 3.6 Hz), 140.12, 140.09, 137.3, 136.4, 135.7 (d, J_{CP} = 2.6 Hz), 134.4 (d, J_{CP} = 3.6 Hz), 130.2 (two peaks are overlapped), 129.0, 128.2, 123.5, 123.0, 117.8 (d, J_{CP} = 4.1 Hz), 117.5 (d, J_{CP} = 4.1 Hz), 55.5 (d, J_{CP} = 6.2 Hz), 54.8 (d, J_{CP} = 2.1 Hz), 36.1, 36.0, 34.3, 32.3 (many peaks are overlapped), 32.2 (many peaks are overlapped), 31.4, 31.1, 30.0 (many peaks are overlapped), 29.7 (many peaks are overlapped), 28.2, 23.0 (many peaks are overlapped), 14.5 (many peaks are overlapped) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) 109.9, -13.5 ppm; MS (ESI) *m/z*: 1748 $[M+Na]^+$; IR (neat): 2917, 2849, 1479, 1399, 1328, 1041 cm^{-1}; HRMS (ESI) calcd for $C_{90}H_{118}AuClN_4O_{11}P_2Na$: 1747.7519 $[M+Na]^+$, Found: 1747.7491.

Synthesis of 5•AuCl: (Scheme 2). Under a nitrogen atmosphere, to a solution of **5** (70 mg, 0.05 mmol) in toluene (0.5 mL) was added AuCl•$S(CH_3)_2$ (18 mg, 0.06 mmol). After stirred at room temperature for 0.5 h, the reaction mixture was concentrated *in vacuo* to give a crude product as a white solid material. Purification by short-plugged silica-gel column chromatography (eluent, CH_2Cl_2) afforded 71 mg of **5**•AuCl in 87% yield as white powders. For data of **5**•AuCl: ^{1}H NMR (400 MHz, $CDCl_3$) 8.11 (d, *J* = 2.5 Hz, 2H), 8.04 (d, *J* = 2.5 Hz, 2H), 7.38 (s, 2H), 7.32 (s, 2H), 7.23 (s, 2H), 7.22 (s, 2H), 5.76 (t, *J* = 8.2 Hz, 2H), 4.58 (t, *J* = 7.8 Hz, 1H), 4.47 (t, *J* = 7.8 Hz, 1H), 4.10 (d, $^3J_{PH}$ = 9.3 Hz, 3H), 4.07 (d, $^3J_{PH}$ = 6.7 Hz, 3H), 2.30-2.22 (m, 8H), 1.45-1.26 (m, 72H), 0.91-0.86 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 153.8, 153.7, 153.1, 152.9, 145.9 (d, J_{CP} = 6.7 Hz), 144.2, (d, J_{CP} = 2.9 Hz), 140.8 140.4, 137.0, 136.3, 135.4 (d, J_{CP} = 2.2 Hz), 134.1 (d, J_{CP} = 2.9 Hz), 123.4, 122.9, 117.7 (d, J_{CP} = 3.8 Hz), 117.2 (d, J_{CP} = 4.1 Hz), 55.8 (d, J_{CP} = 6.0 Hz), 55.0, 35.8, 35.7, 33.7, 32.0 (many peaks are overlapped), 31.1, 30.9, 29.7 (many peaks are overlapped), 29.65 (many peaks are overlapped), 29.63, 29.4, 27.9, 22.7 (many peaks are overlapped), 14.1 (many peaks are overlapped) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) 109.8, -13.1 ppm; MS (ESI) *m/z*: 1648 $[M+Na]^+$; IR (neat): 2917, 2849, 1479, 1399, 1276, 1141, 1038, 894 cm^{-1}; HRMS (ESI) calcd for $C_{82}H_{114}AuClN_4O_{11}P_2Na$: 1647.7206 $[M+Na]^+$, Found : 1647.7184.

Synthesis of 6•AuCl: (Scheme 2). Under a nitrogen atmosphere, to a solution of **6** (63 mg, 0.05 mmol) in toluene (0.5 mL) was added AuCl•$S(CH_3)_2$ (18 mg, 0.06 mmol). After stirred at room temperature for 0.5 h, the reaction mixture was concentrated *in vacuo* to give a crude product as a white solid material. Purification by short-plugged silica-gel column chromatography (eluent, CH_2Cl_2) afforded 68 mg of **6**•AuCl in 89% yield as white powders. For data of **6**•AuCl: ^{1}H NMR (400 MHz, $CDCl_3$) 7.15 (s, 2H), 7.14 (s, 2H), 6.72 (s, 4H), 5.64 (d, *J* = 7.4 Hz, 2H),

4.73 (d, *J* = 7.4 Hz, 2H), 4.70 (t, *J* = 7.6 Hz, 2H), 4.64 (t, *J* = 7.3 Hz, 1H), 4.49 (t, *J* = 7.3 Hz, 1H), 4.08 (d, $^3J_{PH}$ = 14.0 Hz, 3H), 4.06 (d, $^3J_{PH}$ = 11.4 Hz, 3H), 2.27-2.18 (m, 8H), 1.41-1.26 (m, 72H), 0.90-0.87 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 156.4, 156.1, 146.0 (d, J_{CP} = 6.7 Hz), 144.1 (d, J_{CP} = 4.5 Hz), 140.1, 139.3, 136.0 (d, J_{CP} = 2.9 Hz), 135.0 (d, J_{CP} = 3.8 Hz), 122.1, 122.0, 117.5 (d, J_{CP} = 3.8 Hz), 117.3 (d, J_{CP} = 3.8 Hz), 100.0, 56.4 (d, J_{CP} = 6.2 Hz), 55.1 (d, J_{CP} = 2.9 Hz), 37.0, 36.4, 36.2, 32.6 (many peaks are overlapped), 31.0, 30.8, 30.7, 30.4, 30.34 (many peaks are overlapped), 30.25, 30.0, 28.52, 28.48, 28.4, 23.3 (many peaks are overlapped), 14.8 (many peaks are overlapped) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) 108.9, -13.6 ppm; MS (ESI) *m/z*: 1520 $[M+Na]^+$; IR (neat): 2917, 2849, 1487, 1276, 1021, 969 cm^{-1}; HRMS (ESI) calcd for $C_{76}H_{114}AuClO_{11}P_2Na$: 1519.7083 $[M+Na]^+$, Found : 1519.7070.

Synthesis of 10: (Scheme 3). Under an argon atmosphere, to a solution of the tetra-ol parent cavitand (272 mg, 0.2 mmol) in toluene (2 mL) and DMSO (8 mL) at 55 ºC were added K_2CO_3 (42 mg, 0.3 mmol) and CH_2BrCl (0.052 mL, 0.8 mmol). After stirred at 55 ºC for 1 h, the reaction mixture was allowed to cool to room temperature. The mixture was filtered through a pad of celite (eluent, 40 mL of toluene), and the filtrate was evaporated off. The residue was dissolved in toluene, and dried over Na_2SO_4, and filtered, and concentrated *in vacuo* to give a crude of 373 mg. Purification with silica-gel column chromatography (eluent, toluene/EtOAc 9/1) afforded 125 mg of **10** in 46% yield as white solid materials. Data of **10**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.83-7.78 (m, 4H), 7.57-7.50 (m, 4H), 7.35 (s, 2H), 7.27 (s, 2H), 7.17 (s, 2H), 7.16 (s, 2H), 5.76 (d, *J* = 7.4 Hz, 1H), 5.63 (t, *J* = 8.0 Hz 2H), 4.75 (t, *J* = 8.0 Hz, 1H), 4.32 (t, *J* = 8.0 Hz, 1H), 4.16 (d, *J* = 7.4 Hz, 1H), 2.26-2.25 (m, 8H), 1.43-1.28 (m, 72H), 0.90-0.87 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 155.6, 153.4, 153.1, 152.6, 152.3, 151.6, 140.1, 139.6, 138.7, 136.1, 131.4, 129.8, 129.7, 129.0, 128.3, 127.9, 124.7, 121.9, 117.3, 110.7, 100.0, 36.8, 34.3, 33.9, 32.4, 32.3 (many peaks are overlapped), 30.24, 30.19, 30.16, 30.12 (many peaks are overlapped), 30.09, 29.8, 28.4, 28.3, 23.1 (many peaks are overlapped), 14.5 (many peaks are overlapped) ppm; MS (MALDI-TOF) *m/z*: 1370 $[M]^+$; IR (neat): 2917, 2849, 1487, 1404, 1332, 1157, 969, 763 cm^{-1}; HRMS (MALDI-TOF) calcd for $C_{89}H_{117}N_4O_8$: 1369.8866 $[MH]^+$, Found : 1369.8807.

Synthesis of 3: (Scheme 3). Under an argon atmosphere, to a solution of **10** (137 mg, 0.1 mmol) in refluxing toluene (1 mL) were added $EtN(iPr)_2$ (0.17 mL, 1 mmol) and $P(OCH_3)_3$ (0.09 mL, 0.8 mmol). After stirred at 135 ºC for 4 h, the reaction mixture was allowed to cool to room temperature and whole the volatiles were evaporated off. The residue was purified with silica-gel column chromatography (eluent, hexane/EtOAc 9/1) to yield 68 mg of **3** in 48% as white solid materials (Rf values of **3** and *iso*-**3** in eluent of hexane/EtOAc=4/1 are 0.45 and 0.29, respectively). The isomeric compound that oriented P-OMe inwardly was obtained in 18 mg (13% yield). Data of **3**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.85-7.80 (m, 4H), 7.56-7.54 (m, 4H), 7.35 (s, 2H), 7.32 (s, 2H), 7.22 (s, 2H), 7.21 (s, 2H), 5.72 (d, *J* = 7.4 Hz, 1H), 5.71 (t, *J* = 8.0 Hz 2H), 4.70 (t, *J* = 8.0 Hz, 1H), 4.54 (d, *J* = 7.7 Hz, 1H), 4.15 (d, *J* = 7.4 Hz 1H), 3.97 (d, $^3J_{PH}$ = 8.8 Hz 3H), 2.29-2.25 (m, 8H), 1.45-1.28 (m, 72H), 0.91-0.87 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 155.9, 153.24, 153.21, 152.9, 152.2, 147.1 (d, J_{CP} = 5.5 Hz), 140.10, 140.08, 138.5, 137.4 (d, J_{CP} = 2.6 Hz), 135.9, 135.7, 129.74 , 129.71, 128.4, 128.3, 123.6, 122.1, 117.6, 117.3, 99.9, 50.6 (d, J_{CP} = 3.8 Hz), 36.8, 36.2, 34.4, 32.3, (many peaks are overlapped), 29.8, 28.4, 28.32 (many peaks are overlapped), 28.27, 23.0 (many peaks are overlapped), 14.5 (many peaks are overlapped) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) 127.4 ppm; MS (MALDI-TOF) *m/z*: 1430 $[MH]^+$; IR (neat): 2921, 2849, 1479, 1395, 1324, 1157, 1029, 754 cm^{-1}; HRMS (MALDI-TOF) calcd for $C_{90}H_{118}N_4O_9P$: 1429.8631 $[MH]^+$, Found : 1429.8582. Data of *iso*-**3** that orients $POC\underline{H}_3$ inwardly: ^{1}H NMR (400 MHz, $CDCl_3$) 7.85-7.82 (m, 2H), 7.77-7.75 (m, 2H), 7.36-7.33 (m, 4H), 7.31 (s, 2H), 7.23 (s, 2H), 7.20 (s, 2H), 7.16 (s, 2H), 5.72 (d, *J* = 7.4 Hz, 1H), 5.70 (t, *J* = 8.2 Hz 2H), 4.72 (t, *J* = 8.1 Hz, 1H), 4.51 (d, *J* = 7.9 Hz, 1H), 4.23 (d, *J* = 7.4 Hz 1H), 3.22 (d, $^3J_{PH}$ = 12.8 Hz 3H), 2.27-2.22 (m, 8H), 1.44-1.27 (m, 72H), 0.92-0.87 (m, 12H) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) 109.7 ppm.

Synthesis of 3•AuCl: (Scheme 3). Under a nitrogen atmosphere, to a solution of **3** (21 mg, 0.015 mmol) in toluene (0.5 mL) was added $AuCl•S(CH_3)_2$ (5.3 mg, 0.018 mmol). After stirred at room temperature for 0.5 h, the reaction mixture was concentrated *in vacuo* to give a crude product as a white solid material. Purification by short-plugged silica-gel column chromatography (eluent, CH_2Cl_2) afforded 22 mg of **3**•AuCl in 88% yield as white powders.. For data of **3**•AuCl: ^{1}H NMR (400 MHz, $CDCl_3$) 7.96-7.93 (m, 2H), 7.84-7.81 (m, 2H), 7.63-7.61 (m, 2H), 7.60 (s, 2H), 7.58-7.57 (m, 2H), 7.54 (s, 2H), 7.32 (s, 2H), 7.29 (s, 2H), 5.77 (t, *J* = 8.1 Hz, 2H), 5.68 (d, *J* = 7.6 Hz, 1H), 4.74 (t, *J* = 8.0 Hz, 1H), 4.55 (t, *J* = 8.2 Hz, 1H), 4.45 (d, *J* = 7.6 Hz, 1H), 4.20 (d, $^3J_{PH}$ = 13.6 Hz, 3H), 2.37-2.28 (m, 8H), 1.47-1.30 (m, 72H), 0.95-0.90 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 156.0, 153.0, 152.9, 152.5, 152.0, 143.9 (d, J_{CP} = 3.6 Hz), 140.20, 140.18, 138.8, 138.7 (d, J_{CP} = 1.9 Hz), 136.0 (d, J_{CP} = 2.9 Hz), 134.8, 130.1 , 130.0, 129.0, 128.0, 123.1, 122.3, 118.0, 117.7 (d, J_{CP} = 4.3 Hz), 99.5, 55.1 (d, J_{CP} = 3.8 Hz), 36.7, 36.1, 34.3, 32.3, (many peaks are overlapped), 32.2, 31.3, 30.9, 30.09, 30.05 (many peaks are overlapped), 29.8 (many peaks are overlapped), 28.30, 28.27, 28.24, 23.0 (many peaks are overlapped), 14.5 (many peaks are overlapped) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) 108.5 ppm; MS (ESI) *m/z*: 1684 $[M+Na]^+$; IR (neat): 2925, 2849, 1483, 1404, 1328, 1157, 759 cm^{-1}; HRMS (ESI) calcd for $C_{90}H_{117}AuClN_4O_9PNa$: 1683.7804 $[M+Na]^+$, Found : 1683.7833.

Representative Procedure of Hydration Reactions of 1-Phenyl-1-Butyne 7a: (Table 2, entry 1). Under an argon atmosphere, to a solution of 1-phenyl-1-butyne (0.28 mL, 2.0 mmol) in toluene (1 mL) and H_2O (0.05 mL, 2.5 mmol) was added **2**•AuCl (17 mg, 0.01 mmol). The mixture was stirred at room temperature for 5 min, then AgOTf (3 mg, 0.012 mmol) was added, and the whole system was dipped in the 50 ºC pre-heated oil-bath. After stirred for 1 h, the reaction was allowed to cool to room temperature. Purification of the reaction mixture through a short-plugged silica-gel column chromatography (toluene only) and the following careful evaporation of the toluene eluent afforded yellow oil of mixtures that consisted of 1-phenyl-2-butanone **9a** (260 mg, 88% yield) and 1-phenyl-1-butanone **8a** (6.0 mg, 2% yield). Data for **9a** was as follows, and that was identical to the commercially available authentic sample; ^{1}H NMR (400 MHz, $CDCl_3$) 7.35-7.20 (m, 5H), 3.69 (s, 2H), 2.48 (q, *J* = 7.3 Hz, 2H), 1.03 (t, *J* = 7.3 Hz, 3H) ppm. Data for **8a** was as follows, and that was identical to the commercially available sample; ^{1}H NMR (400 MHz, $CDCl_3$) 7.96 (d, *J* = 7.8 Hz, 2H), 7.55 (dd, *J* = 7.8 Hz, *J* = 7.8 Hz, 1H), 7.46 (dd, *J* = 7.8 Hz, *J* = 7.8 Hz, 2H), 2.95 (t, *J* = 7.4 Hz, 1H), 1.78 (qt, *J* = 7.4 Hz, *J* = 7.4 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H) ppm.

Representative Procedure of Hydration Reactions of 2-Octyne 7d, in which [D_8]toluene was used: (Table 2, entry 14). Under an argon atmosphere, to a solution of 2-octyne (0.29 mL, 2.0 mmol) in toluene (1 mL) and H_2O (0.05 mL, 2.5 mmol) was added **2**•AuCl (17 mg, 0.01 mmol). The mixture was stirred at room temperature for 5 min, then AgOTf (3 mg, 0.012 mmol) was added, and the whole system was dipped in the 50 ºC pre-heated oil-bath. After stirred for 1 h, the reaction was allowed to cool to room temperature. Purification of the reaction mixture through a short-plugged silica-gel column chromatography in which a Pasteur pipette and an eluent of toluene-d_8 were used gave a colorless C_7D_8 solution. ^{1}H NMR explained that the product was consisted of 88% **9d** and 12% **8d**. The ^{1}H NMR data of **9d** and **8d** were identical to the commercially available authentic sample. The stack of those ^{1}H NMR spectra is shown in Figure 1S of Supporting Information.

Supporting Information (see footnote in the first page of this article): The ^{1}H NMR and ^{13}C NMR spectra of all new compounds.

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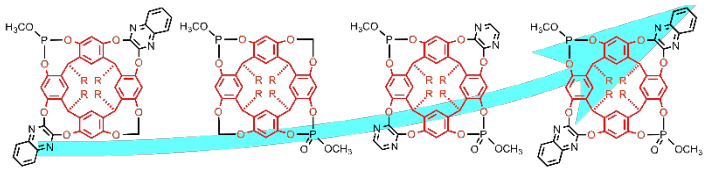

Structure-Activity Relationship for Cavitand Catalysis

Supramolecular catalysis was elucidated through a comparison with corresponding model catalysts that weekend the caged architecture and functionality. The diquinoxaline-spanned resorcin[4]arene bearing Lewis acid and base selectively catalyzed alkyne hydration, in which we investigated structure-activity relationships and found the significant skeletons.

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Selective catalytic hydration of alkynes using Au-cavitands: a study in structure-activity relationship