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Selective Catalytic Hydration of Alkynes in the Presence of Au-Cavitands: A Study in Structure–Activity Relationships

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Abstract: The effects of the catalytic cavities in gold-functionalized cavitands in the hydration of internal alkynes have been studied. Variations on cavitand structures revealed 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 system provides a well-defined compartment, in which a cationic Au ion activates an internal alkyne for conversion into 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 cavitand walls include replacement of quinoxaline components with pyrazine or methylene units. Variation of the P=O center was accomplished with methylene or quinoxaline moieties. All variants displayed lower catalytic activity or selectivity, allowing us to confirm the significance both of an internal cavity and of an activation site for water.

Introduction

Cram et al. suggested in 1982 that the class name *cavitand* was apt for synthetic organic compounds that contain *enforced cavities* large enough to accommodate simple molecules or ions.[1] Since that important classification, cavitand research has taken many paths. One of these has led to the emergence of catalyst centers being positioned around or inside the enclosed space. The resemblance to enzymes is significant because the presence of a confined space and an active site are present in supramolecular complexes of both classes.[2,3] Four classes of platform (calixarenes,[4] cyclotriveratrylenes,[5] cyclodextrins,[6] and resorcinarenes[7]) have received attention. In particular, 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 reported examples of successful catalytic cavitands. Embedding metal centers with inward orientation presents several synthetic challenges.[8] Consequently, knowledge of how these supramolecular chemistries might contain features and principles that will be significant to the advancement of chemical catalysis remains limited.

We recently synthesized a cavitand in the form of **1**·AuCl, a di-quinoxaline-spanned resorcin[4]arene in which P–Au and P=O are directed inwardly [Figure 1(a)]. We found it efficiently catalyzes regioselective hydration of unsymmetrical internal alkynes such as simple oct-3-yne and 1-phenylbut-1-yne.[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) the Lewis basic P=O system hydrogen bonds with a water molecule,[11] and 3) side-chain recognition is based on length and selective fit. Our initial report led us to attempt to determine more detailed structure–activity relationships. Our hypotheses were supported by our initial screening with **1**·AuCl: oct-3-yne, for example, is hydrated at the 3-position to

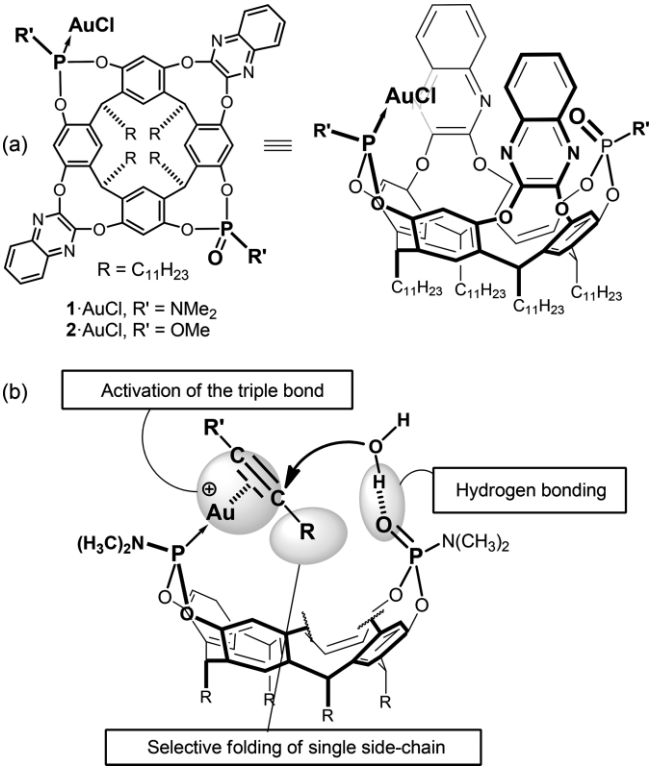

Figure 1. (a) Mono-AuCl cavitands **1**·AuCl and **2**·AuCl, and (b) working hypothesis of three points: (1) coordination of Au^+ toward an alkyne triple bond, (2) hydrogen bonding between P=O and H_2O, and (3) selective folding of single side chain (the two quinoxaline walls are omitted for ease of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

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yield octan-3-one, in 91 % yield, rather than octan-4-one.[9] We speculated that the π-surface formed by the two quinoxaline walls plays a role either in recognition or in stabilization of intermediates. Previously these walls had been observed to play an essential role in alkyne–alkyne cross-coupling with two facing Au centers.[12] The role of the P=O group also needed to be clarified. This could 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, which also supports gold. Thus, **2**·AuCl represents the starting point for this study, as opposed to our initial catalyst with P–$N(CH_3)_2$ units (**1**·AuCl) [Figure 1(a)].

Here we report the synthesis of **2**·AuCl and of the corresponding variants **3**·AuCl, **4**·AuCl, **5**·AuCl, and **6**·AuCl (Figure 2). We include a direct comparison of their catalytic capabilities in the chemical transformations illustrated in Scheme 1. Compounds **3**·AuCl and **4**·AuCl are variations in which we replaced the P=O group of **2** with methylene or quinoxaline substructures. In **5**·AuCl the height of the walls is reduced: two pyrazine components are now present in place of the quinoxaline units. In **6**·AuCl the walls are removed completely. We anticipated that comparative experiments would test the hypothesis of Figure 1(b) and also enhance the value of the skeletal structure of **2** in chemical catalysis.[13]

Results and Discussion

We synthesized the 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** (37 %), **5** (48 %), and **6** (32 %).[9] Subsequent complexation with AuCl·$S(CH_3)_2$ occurred smoothly, forming **2**·AuCl, **5**·AuCl, and **6**·AuCl in 86 %, 87 %, and 89 % yields, respectively.

For the synthesis of **3**·AuCl, the three-step route illustrated in Scheme 3 was used: firstly, the tetraol platform was treated with CH_2BrCl to form **10** in 46 % yield. Treatment of **10** with $P(OCH_3)_3$ then gave two isomeric compounds. In these, the $POCH_3$ moiety is oriented outwards in the desired **3** (48 %) and

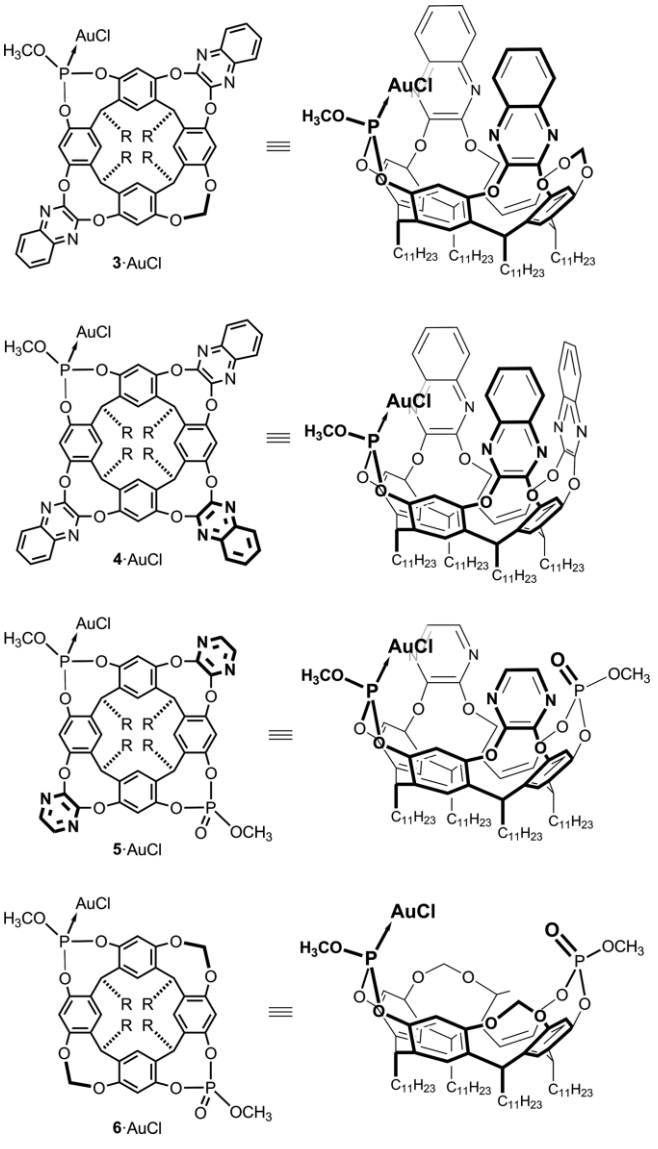
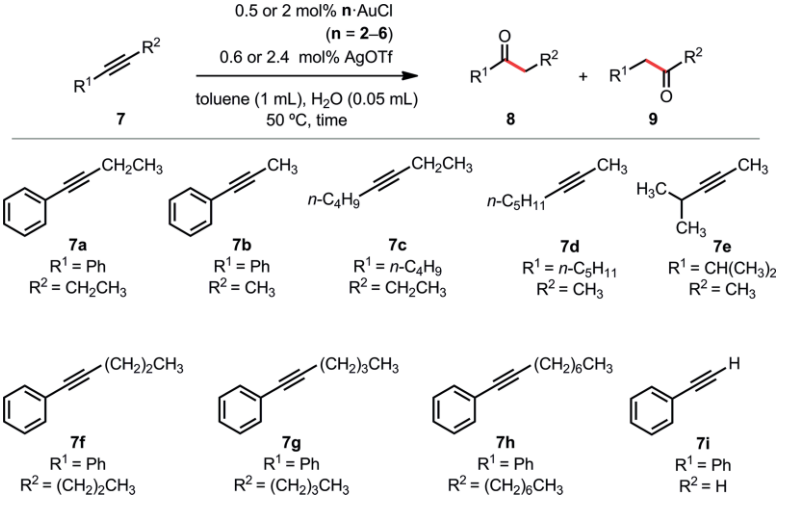
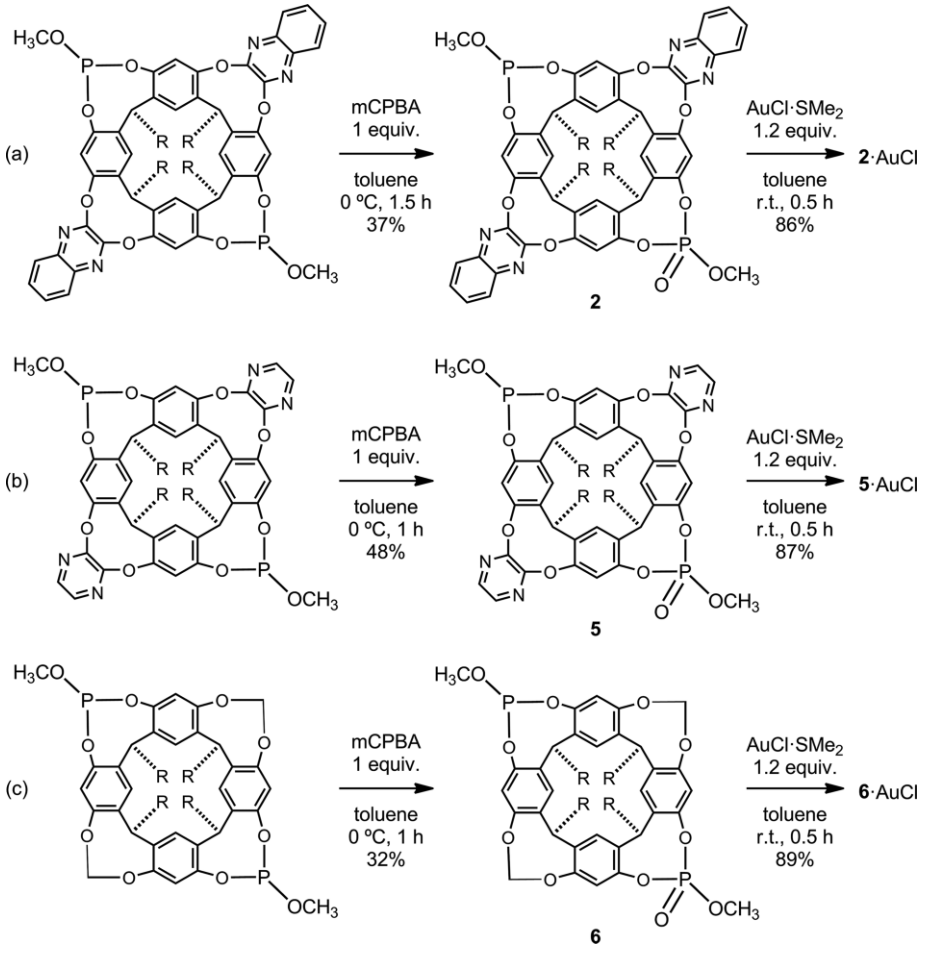


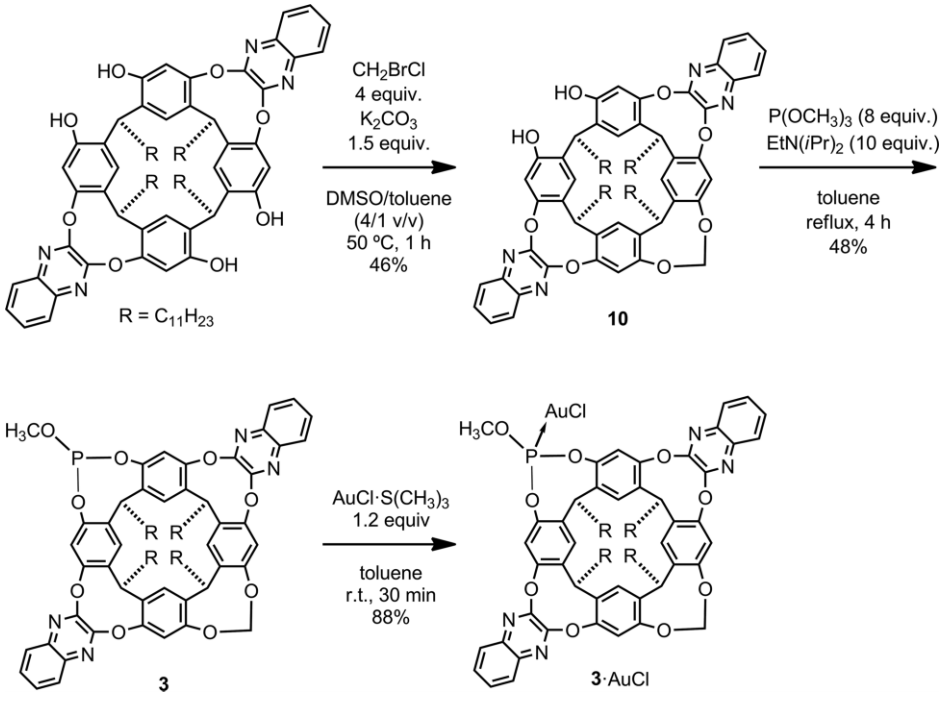
Figure 2. The model compounds **3**·AuCl, **4**·AuCl, **5**·AuCl, and **6**·AuCl (R = $C_{11}H_{23}$).



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



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



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

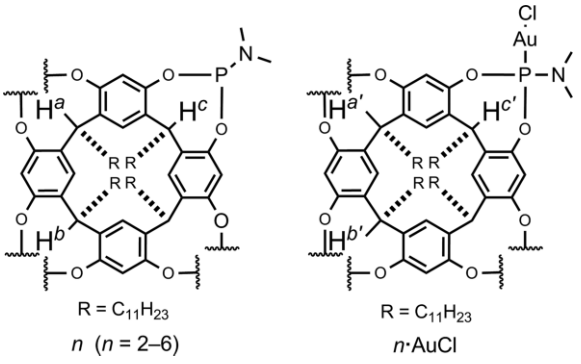
inwards in *iso*-**3** (13 % yield). The ^{1}H NMR chemical shift of the POCH_3 group in **3** is located at δ = 3.97 ppm for **3**; in the case of *iso*-**3** it is at 3.22 ppm. The anisotropic effect of the internal π-cloud shifts the inside OCH_3 of *iso*-**3** upfield in relation to that of **3**. The clean complexation between **3** and AuCl·S$(CH_3)_2$ proceeded in 88 % yield.

We reported the synthesis of **4**·AuCl previously.[14]

We made the following observations about the solution dynamics of **2**–**6** and **2**·AuCl–**6**·AuCl. Four-walled quinoxaline cavitands are known to fluctuate between vase (closed) and kite (open) conformations, and reports on the effects of solvent and acid have been published.[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 reside in an electronic environment different from that of 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 methine groups in comparison with the parent **2**. For **4**, protons H^a and H^b are consistent with a vase shape. For **5** and **6**, no major structural perturbations from a vase shape are observed. Thus, these cavitands exist in vase-like conformations when dissolved in toluene, with the Au metal centers pointing inward. This is consistent with our previous work, which includes solid-state single-crystal X-ray data.[12,14]

With a collection of new cavitands prepared, we evaluated the differences in reactivities between **2**, **3**, and **4** in the hydration of alkynes **7a**–**e** (Scheme 1). The results of these experiments are summarized in Table 2, revealing the role of the P=O substructure of **2**. As reported in Entry 1, **2** gave **9a** in 88 % yield, together with minor isomer **8a** in 2 % yield. Entries 2 and 3 show that **3** did not catalyze the hydration even in the presence of external O=PPh_3. Use of a prolonged reaction time (Entry 4) ultimately gave a 71 % yield of **9a** and a 12 % yield of **8a**. Entries 5–7 show that the three-walled **4** only gave a 38 % yield of **9a** after prolonged overnight reaction with external O=PPh_3. In Entries 8–10, in which alkyne **7b** was used, the contrast between the results obtained with **2** and those obtained with **3** and **4** were more pronounced. This trend continued with alkynes **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 that achieved with **2**. Thus, the covalently appended P=O group present in **2** is essential for efficient and selective hydration.

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



n	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.

Table 2. Evaluation of reactivities of **2**·AuCl, **3**·AuCl, and **4**·AuCl conducted as shown in Scheme 1.[a]

Entry	Alkyne	***n***·AuCl [mol-%]	n	O=PPh_3 [mol-%]	*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**, [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 purified by short-plug 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 the quinoxaline walls in **2**. Evaluation of the differences in reactivities between **2**, **5**, and **6** was carried out through hydration of **7a**–**i**, and selected results are summarized in Table 3.[16] In the case of **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 to **2**·AuCl, with **7b** and **7a** undergoing selective hydration reactions (Entries 4–5). On the other hand, unwalled **6**·AuCl showed a different pattern of reactivity: only **7a** underwent a selective reaction, and other substrates were almost completely unhydrated (Entries 7–9). It is noteworthy that the presence of pyrazine and quinoxaline walls allow **7b** to undergo hydration (Entries 2 and 5). These results indicate that all of the walls enhance the reactivity and selectivity.

Table 3. Evaluation of reactivities of **2**·AuCl, **5**·AuCl, and **6**·AuCl conducted as shown in 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 ^1H NMR analyses on the basis of samples purified by short-plug silica-gel column chromatography (eluent: [D_8]toluene). [c] Unreacted **7**.

Conclusions

In conclusion, we have studied the catalytic capability of **2**·AuCl in the selective hydration of alkynes by preparing four other kinds of cavitands – **3**, **4**, **5**, and **6** – and examining structure–activity relationships. Comparative study using these model catalysts strongly suggests two salient features. Firstly, a P=O group covalently attached to the resorcin[4]arene core significantly facilitates the addition of the water molecule to the alkyne triple bond. This proximity effect was clearly shown in experiments in which this group was absent. Secondly, 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.[17–19] This is a consequence of such a confined space in **2**, because this space would govern the shape of the transition state. These results illustrate that the quinoxaline-spanned resorcin[4]arene skeleton can be specifically designed to elicit selective catalysis. Previously, this level of control with use of a supramolecular architecture had not been achieved, to the best of 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 argon or nitrogen and under 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 60 F_{254}. Column chromatography was carried out with silica gel 60*n* (Kanto Chemical Co.). LRMS and HRMS were measured by TOF (time of flight) MS (MADI-TOF or LCMS-IT-TOF) and DART (Direct Analysis in Real Time) MS. ^1H and ^{13}C NMR spectra were recorded with a 5 mm QNP probe at 400 MHz and 100 MHz, respectively. Chemical shifts are reported as δ values (ppm) with reference to residual solvent signals [^1H 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): A cooled toluene solution of *meta*-chloroperbenzoic acid (mCPBA, 75 %, 46 mg, 0.2 mmol) was slowly added over 3 min to the parent bisphosphite (296 mg, 0.2 mmol) in toluene (8 mL) at 0 °C. After stirring at 0 °C for 1.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (4 mL), and the mixture was stirred at ambient temperature for 40 min. It was then transferred into a 100 mL separating funnel, washed with water (20 mL) and brine (20 mL), dried with Na_2SO_4, and concentrated in vacuo to give crude **2** (285 mg) as a white solid. Purification by short-plug column chromatography (SiO_2, toluene/EtOAc 9:1) yielded **2** (112 mg, 37 %) as a white solid powder. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.81 (m, 4 H), 7.54–7.51 (m, 4 H), 7.47 (s, 2 H), 7.40 (s, 2 H), 7.24 (s, 2 H), 7.17 (s, 2 H), 5.74 (t, J = 8.2 Hz, 2 H), 4.59–4.55 (m, 2 H), 4.09 (d, $^3J_{P,H}$ = 11.4 Hz, 3 H), 3.94 (d, $^3J_{P,H}$ = 8.8 Hz, 3 H), 2.36–2.20 (m, 8 H), 1.45–1.28 (m, 72 H), 0.91–0.87 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0, 152.9, 152.8 (d, $J_{C,P}$ = 1.4 Hz), 152.6, 148.0 (d, $J_{C,P}$ = 5.0 Hz), 146.2 (d, $J_{C,P}$ = 6.7 Hz), 140.13, 140.09, 137.3, 137.2, 134.7, 134.1 (d, $J_{C,P}$ = 3.8 Hz), 129.8, 129.7, 128.5, 128.3, 123.3, 122.8, 118.0, 117.1, 56.1 (d, $J_{C,P}$ = 6.2 Hz), 50.2 (d, $J_{C,P}$ = 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, $CDCl_3$): δ = 127.3, –13.5 ppm. IR (neat): $\tilde{\nu}$ = 2917, 2849, 1479, 1399, 1328, 1025 cm^{-1}. MS (DART-TOF): m/z = 1494 $[M + H]^+$. HRMS (DART-TOF): calcd. for $C_{90}H_{119}N_4O_{11}P_2$ $[M + H]^+$ 1493.8345; found 1493.8427. $C_{90}H_{118}N_4O_{11}P_2$ (1493.89): calcd. C 72.36, H 7.96, N 3.75; found C 72.35, H 7.87, N 3.78.

Synthesis of 5: A cooled toluene solution of mCPBA (75 %, 30 mg, 0.13 mmol) was slowly added under argon to a solution of the parent bisphosphite (174 mg, 0.13 mmol) in toluene (5.2 mL) at 0 °C. After stirring at 0 °C for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (2.6 mL), and the mixture was stirred at ambient temperature for 45 min. It was transferred into a separating funnel, washed with water (10 mL) and brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo to give crude **5** (167 mg) as a white solid. Purification by silica-gel column chromatography (toluene/EtOAc 2:1) yielded **5** (86 mg, 48 %) as a white powder. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 2.6 Hz, 2 H), 8.01 (d, J = 2.6 Hz, 2 H), 7.32 (s, 2 H), 7.26 (s, 2 H), 7.24 (s, 2 H), 7.17 (s, 2 H), 5.72 (t, J = 8.2 Hz, 2 H), 4.57–4.54 (m, 2 H), 4.07 (d, $^3J_{P,H}$ = 11.4 Hz, 3 H), 3.91 (d, $^3J_{P,H}$ = 9.0 Hz, 3 H), 2.28–2.18 (m, 8 H), 1.14–1.27 (m, 72 H), 0.91–0.87 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.7, 154.5, 153.1 (d, $J_{C,P}$ = 1.7 Hz), 152.9, 148.0 (d, $J_{C,P}$ = 5.2 Hz), 146.2 (d, $J_{C,P}$ = 6.7 Hz), 140.4, 140.2, 137.4 (d, $J_{C,P}$ = 2.6 Hz), 137.3 (d, $J_{C,P}$ = 2.2 Hz), 134.8, 134.1 (d, $J_{C,P}$ = 3.6 Hz), 123.5, 123.0, 117.9 (d, $J_{C,P}$ = 2.4 Hz),

117.1 (d, $J_{C,P}$ = 3.6 Hz), 56.1 (d, $J_{C,P}$ = 6.0 Hz), 50.3 (d, $J_{C,P}$ = 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, $CDCl_3$): δ = 128.0, –13.5 ppm. IR (neat): $\tilde{\nu}$ = 2925, 2853, 1479, 1395, 1296, 1137, 1029 cm^{-1}. MS (MALDI-TOF): *m/z* = 1394 [M + H]$^+$. HRMS (MALDI-TOF): calcd. for $C_{82}H_{115}N_4O_{11}P_2$ [M + H]$^+$ 1393.8032; found 1393.8079.

Synthesis of 6: A cooled toluene solution of mCPBA (75 %, 198 mg, 047 mmol) was slowly added under argon to a solution of the parent bisphosphite (592 mg, 0.47 mmol) in toluene (18.8 mL) at 0 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ (9.4 mL), and the mixture was stirred at ambient temperature for 35 min. It was transferred into a separating funnel, washed with water (10 mL) and brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo to give crude **6** (594 mg) as a white solid. Purification by silica-gel column chromatography (toluene/EtOAc 4:1) yielded **6** (192 mg, 32 %) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (s, 2 H), 7.09 (s, 2 H), 6.65 (s, 2 H), 6.60 (s, 2 H), 5.66 (d, *J* = 7.3 Hz, 2 H), 4.74 (t, *J* = 8.1 Hz, 2 H), 4.66 (d, *J* = 7.3 Hz, 2 H), 4.60–4.55 (m, 2 H), 4.05 (d, $^3J_{P,H}$ = 11.4 Hz, 3 H), 3.90 (d, $^3J_{P,H}$ = 9.1 Hz, 3 H), 2.23–2.18 (m, 8 H), 1.42–1.27 (m, 72 H), 0.90–0.87 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7 (d, $J_{C,P}$ = 1.4 Hz), 155.4, 147.3 (d, $J_{C,P}$ = 4.8 Hz), 145.6 (d, $J_{C,P}$ = 7.4 Hz), 139.8, 137.5, 137.2, 134.1 (d, $J_{C,P}$ = 3.8 Hz), 121.7, 121.2, 117.7, 116.7 (d, $J_{C,P}$ = 4.1 Hz), 99.4, 56.0 (d, $J_{C,P}$ = 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, $CDCl_3$): δ = 127.3, –13.5 ppm. IR (neat): $\tilde{\nu}$ = 2917, 2849, 1487, 1451, 1308, 1281, 1034, 961 cm^{-1}. MS (DART-TOF): *m/z* = 1283 [M + NH_4]$^+$. 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: AuCl·$S(CH_3)_2$ (18 mg, 0.06 mmol) was added under argon to a 10 mL one-necked round-bottomed flask charged with a solution of **2** (75 mg, 0.05 mmol) in toluene (0.5 mL). After stirring at room temperature for 30 min, the reaction mixture was concentrated in vacuo to give a crude product. This was purified by short-plug column chromatography (20 mL hexane/EtOAc 2:1) to yield **2**·AuCl (75 mg in 86 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (dd, *J* = 7.8, 1.8 Hz, 2 H), 7.83 (dd, *J* = 7.7, 2.0 Hz, 2 H), 7.58–7.51 (m, 6 H), 7.43 (s, 2 H), 7.22 (s, 4 H), 5.78 (t, *J* = 8.1 Hz, 2 H), 4.59 (t, *J* = 7.9 Hz, 1 H), 4.51 (t, *J* = 8.0 Hz, 1 H), 4.13 (d, $^3J_{P,H}$ = 13.9 Hz, 3 H), 4.09 (d, $^3J_{P,H}$ = 11.4 Hz, 3 H), 2.31–2.25 (m, 8 H), 1.45–1.27 (m, 72 H), 0.92–0.86 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1 (d, $J_{C,P}$ = 1.7 Hz), 152.9 (d, $J_{C,P}$ = 1.7 Hz), 152.34, 152.30, 146.3 (d, $J_{C,P}$ = 6.9 Hz), 144.5 (d, $J_{C,P}$ = 3.6 Hz), 140.12, 140.09, 137.3, 136.4, 135.7 (d, $J_{C,P}$ = 2.6 Hz), 134.4 (d, $J_{C,P}$ = 3.6 Hz), 130.2 (two peaks are overlapped), 129.0, 128.2, 123.5, 123.0, 117.8 (d, $J_{C,P}$ = 4.1 Hz), 117.5 (d, $J_{C,P}$ = 4.1 Hz), 55.5 (d, $J_{C,P}$ = 6.2 Hz), 54.8 (d, $J_{C,P}$ = 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, $CDCl_3$): δ = 109.9, –13.5 ppm. IR (neat): $\tilde{\nu}$ = 2917, 2849, 1479, 1399, 1328, 1041 cm^{-1}. MS (ESI): *m/z* = 1748 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{90}H_{118}AuClN_4O_{11}P_2Na$ [M + Na]$^+$ 1747.7519; found 1747.7491.

Synthesis of 5·AuCl: AuCl·$S(CH_3)_2$ (18 mg, 0.06 mmol) was added under nitrogen to a solution of **5** (70 mg, 0.05 mmol) in toluene (0.5 mL). After stirring at room temperature for 0.5 h, the reaction mixture was concentrated in vacuo to give a crude product as a white solid. Purification by short-plug silica-gel column chromatography (eluent CH_2Cl_2) afforded **5**·AuCl (71 mg, 87 %) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 2.5 Hz, 2 H), 8.04 (d, *J* = 2.5 Hz, 2 H), 7.38 (s, 2 H), 7.32 (s, 2 H), 7.23 (s, 2 H), 7.22 (s, 2 H), 5.76 (t, *J* = 8.2 Hz, 2 H), 4.58 (t, *J* = 7.8 Hz, 1 H), 4.47 (t, *J* = 7.8 Hz, 1 H), 4.10 (d, $^3J_{P,H}$ = 9.3 Hz, 3 H), 4.07 (d, $^3J_{P,H}$ = 6.7 Hz, 3 H), 2.30–2.22 (m, 8 H), 1.45–1.26 (m, 72 H), 0.91–0.86 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.8, 153.7, 153.1, 152.9, 145.9 (d, $J_{C,P}$ = 6.7 Hz), 144.2, (d, $J_{C,P}$ = 2.9 Hz), 140.8 140.4, 137.0, 136.3, 135.4 (d, $J_{C,P}$ = 2.2 Hz), 134.1 (d, $J_{C,P}$ = 2.9 Hz), 123.4, 122.9, 117.7 (d, $J_{C,P}$ = 3.8 Hz), 117.2 (d, $J_{C,P}$ = 4.1 Hz), 55.8 (d, $J_{C,P}$ = 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, $CDCl_3$): δ = 109.8, –13.1 ppm. IR (neat): $\tilde{\nu}$ = 2917, 2849, 1479, 1399, 1276, 1141, 1038, 894 cm^{-1}. MS (ESI): *m/z* = 1648 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{82}H_{114}AuClN_4O_{11}P_2Na$ [M + Na]$^+$ 1647.7206; found 1647.7184.

Synthesis of 6·AuCl: AuCl·$S(CH_3)_2$ (18 mg, 0.06 mmol) was added under nitrogen to a solution of **6** (63 mg, 0.05 mmol) in toluene (0.5 mL). After stirring at room temperature for 0.5 h, the reaction mixture was concentrated in vacuo to give a crude product as a white solid. Purification by short-plug silica-gel column chromatography (eluent CH_2Cl_2) afforded **6**·AuCl (68 mg, 89 %) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (s, 2 H), 7.14 (s, 2 H), 6.72 (s, 4 H), 5.64 (d, *J* = 7.4 Hz, 2 H), 4.73 (d, *J* = 7.4 Hz, 2 H), 4.70 (t, *J* = 7.6 Hz, 2 H), 4.64 (t, *J* = 7.3 Hz, 1 H), 4.49 (t, *J* = 7.3 Hz, 1 H), 4.08 (d, $^3J_{P,H}$ = 14.0 Hz, 3 H), 4.06 (d, $^3J_{P,H}$ = 11.4 Hz, 3 H), 2.27–2.18 (m, 8 H), 1.41–1.26 (m, 72 H), 0.90–0.87 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4, 156.1, 146.0 (d, $J_{C,P}$ = 6.7 Hz), 144.1 (d, $J_{C,P}$ = 4.5 Hz), 140.1, 139.3, 136.0 (d, $J_{C,P}$ = 2.9 Hz), 135.0 (d, $J_{C,P}$ = 3.8 Hz), 122.1, 122.0, 117.5 (d, $J_{C,P}$ = 3.8 Hz), 117.3 (d, $J_{C,P}$ = 3.8 Hz), 100.0, 56.4 (d, $J_{C,P}$ = 6.2 Hz), 55.1 (d, $J_{C,P}$ = 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, $CDCl_3$): δ = 108.9, –13.6 ppm. IR (neat): $\tilde{\nu}$ = 2917, 2849, 1487, 1276, 1021, 969 cm^{-1}. MS (ESI): *m/z* = 1520 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{76}H_{114}AuClO_{11}P_2Na$ [M + Na]$^+$ 1519.7083; found 1519.7070.

Synthesis of 10 (Scheme 3): K_2CO_3 (42 mg, 0.3 mmol) and CH_2BrCl (0.052 mL, 0.8 mmol) were added under argon to a solution of the tetraol parent cavitand (272 mg, 0.2 mmol) in toluene (2 mL) and DMSO (8 mL) at 55 °C. After stirring at 55 °C for 1 h, the reaction mixture was allowed to cool to room temperature. The mixture was filtered through a pad of celite (eluent toluene, 40 mL), and the filtrate was evaporated off. The residue was dissolved in toluene, dried with Na_2SO_4, filtered, and concentrated in vacuo to give crude **10** (373 mg). Purification by silica-gel column chromatography (eluent toluene/EtOAc 9:1) afforded **10** (125 mg, 46 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.78 (m, 4 H), 7.57–7.50 (m, 4 H), 7.35 (s, 2 H), 7.27 (s, 2 H), 7.17 (s, 2 H), 7.16 (s, 2 H), 5.76 (d, *J* = 7.4 Hz, 1 H), 5.63 (t, *J* = 8.0 Hz, 2 H), 4.75 (t, *J* = 8.0 Hz, 1 H), 4.32 (t, *J* = 8.0 Hz, 1 H), 4.16 (d, *J* = 7.4 Hz, 1 H), 2.26–2.25 (m, 8 H), 1.43–1.28 (m, 72 H), 0.90–0.87 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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. IR (neat): $\tilde{\nu}$ = 2917, 2849, 1487, 1404, 1332, 1157, 969,

763 cm^{-1}. MS (MALDI-TOF): *m/z* = 1370 $[M]^+$. HRMS (MALDI-TOF): calcd. for $C_{89}H_{117}N_4O_8$ $[M + H]^+$ 1369.8866; found 1369.8807.

Synthesis of 3: $EtN(iPr)_2$ (0.17 mL, 1 mmol) and $P(OCH_3)_3$ (0.09 mL, 0.8 mmol) were added under argon to a solution of **10** (137 mg, 0.1 mmol) in toluene at reflux (1 mL). After stirring at 135 °C for 4 h, the reaction mixture was allowed to cool to room temperature and concentrated. The residue was purified by silica-gel column chromatography (eluent hexane/EtOAc 9:1) to yield **3** (68 mg, 48 %) as a white solid (R_f values of **3** and *iso*-**3** in hexane/EtOAc 4:1 as eluent are 0.45 and 0.29, respectively). The isomeric compound in which P–OMe is oriented inward was also obtained (18 mg, 13 %).

Data for **3**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.80 (m, 4 H), 7.56–7.54 (m, 4 H), 7.35 (s, 2 H), 7.32 (s, 2 H), 7.22 (s, 2 H), 7.21 (s, 2 H), 5.72 (d, *J* = 7.4 Hz, 1 H), 5.71 (t, *J* = 8.0 Hz, 2 H), 4.70 (t, *J* = 8.0 Hz, 1 H), 4.54 (d, *J* = 7.7 Hz, 1 H), 4.15 (d, *J* = 7.4 Hz, 1 H), 3.97 (d, $^3J_{P,H}$ = 8.8 Hz, 3 H), 2.29–2.25 (m, 8 H), 1.45–1.28 (m, 72 H), 0.91–0.87 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 153.24, 153.21, 152.9, 152.2, 147.1 (d, $J_{C,P}$ = 5.5 Hz), 140.10, 140.08, 138.5, 137.4 (d, $J_{C,P}$ = 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, $J_{C,P}$ = 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, $CDCl_3$): δ = 127.4 ppm. IR (neat): $\tilde{\nu}$ = 2921, 2849, 1479, 1395, 1324, 1157, 1029, 754 cm^{-1}. MS (MALDI-TOF): *m/z* = 1430 $[M + H]^+$. HRMS (MALDI-TOF): calcd. for $C_{90}H_{118}N_4O_9P$ $[M + H]^+$ 1429.8631; found 1429.8582.

Data for *iso*-**3**, in which $POCH_3$ is oriented inward: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.82 (m, 2 H), 7.77–7.75 (m, 2 H), 7.36–7.33 (m, 4 H), 7.31 (s, 2 H), 7.23 (s, 2 H), 7.20 (s, 2 H), 7.16 (s, 2 H), 5.72 (d, *J* = 7.4 Hz, 1 H), 5.70 (t, *J* = 8.2 Hz, 2 H), 4.72 (t, *J* = 8.1 Hz, 1 H), 4.51 (d, *J* = 7.9 Hz, 1 H), 4.23 (d, *J* = 7.4 Hz, 1 H), 3.22 (d, $^3J_{P,H}$ = 12.8 Hz, 3 H), 2.27–2.22 (m, 8 H), 1.44–1.27 (m, 72 H), 0.92–0.87 (m, 12 H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 109.7 ppm.

Synthesis of 3·AuCl: $AuCl{\cdot}S(CH_3)_2$ (5.3 mg, 0.018 mmol) was added under nitrogen to a solution of **3** (21 mg, 0.015 mmol) in toluene (0.5 mL). After stirring 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-plug silica-gel column chromatography (eluent CH_2Cl_2) afforded **3·**AuCl (22 mg, 88 %) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.93 (m, 2 H), 7.84–7.81 (m, 2 H), 7.63–7.61 (m, 2 H), 7.60 (s, 2 H), 7.58–7.57 (m, 2 H), 7.54 (s, 2 H), 7.32 (s, 2 H), 7.29 (s, 2 H), 5.77 (t, *J* = 8.1 Hz, 2 H), 5.68 (d, *J* = 7.6 Hz, 1 H), 4.74 (t, *J* = 8.0 Hz, 1 H), 4.55 (t, *J* = 8.2 Hz, 1 H), 4.45 (d, *J* = 7.6 Hz, 1 H), 4.20 (d, $^3J_{P,H}$ = 13.6 Hz, 3 H), 2.37–2.28 (m, 8 H), 1.47–1.30 (m, 72 H), 0.95–0.90 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 153.0, 152.9, 152.5, 152.0, 143.9 (d, $J_{C,P}$ = 3.6 Hz), 140.20, 140.18, 138.8, 138.7 (d, $J_{C,P}$ = 1.9 Hz), 136.0 (d, $J_{C,P}$ = 2.9 Hz), 134.8, 130.1, 130.0, 129.0, 128.0, 123.1, 122.3, 118.0, 117.7 (d, $J_{C,P}$ = 4.3 Hz), 99.5, 55.1 (d, $J_{C,P}$ = 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, $CDCl_3$): δ = 108.5 ppm. IR (neat): $\tilde{\nu}$ = 2925, 2849, 1483, 1404, 1328, 1157, 759 cm^{-1}. MS (ESI): *m/z* = 1684 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{90}H_{117}AuClN_4O_9PNa$ $[M + Na]^+$ 1683.7804; found 1683.7833.

Representative Procedure – Hydration of 1-Phenylbut-1-yne (7a, Table 2, Entry 1): Compound **2·**AuCl (17 mg, 0.01 mmol) was added under argon to a solution of 1-phenylbut-1-yne (0.28 mL, 2.0 mmol) in toluene (1 mL) and H_2O (0.05 mL, 2.5 mmol). The mixture was stirred at room temperature for 5 min, AgOTf (3 mg, 0.012 mmol) was then added, and the whole system was immersed in a 50 °C preheated oil bath. After stirring for 1 h, the mixture was allowed to cool to room temperature. Purification by short-plug silica-gel column chromatography (toluene only) and subsequent careful evaporation of the toluene eluent afforded a yellow oil that consisted of 1-phenylbutan-2-one (**9a**, 260 mg, 88 %) and 1-phenylbutan-1-one (**8a**, 6.0 mg, 2 %). Data for **9a** are as follows, and are identical to those for a commercially available authentic sample. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 5 H), 3.69 (s, 2 H), 2.48 (q, *J* = 7.3 Hz, 2 H), 1.03 (t, *J* = 7.3 Hz, 3 H) ppm. Data for **8a** are as follows, and are also identical to those for a commercially available sample. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.8 Hz, 2 H), 7.55 (dd, *J* = 7.8, *J* = 7.8 Hz, 1 H), 7.46 (dd, *J* = 7.8, *J* = 7.8 Hz, 2 H), 2.95 (t, *J* = 7.4 Hz, 1 H), 1.78 (qt, *J* = 7.4, *J* = 7.4 Hz, 2 H), 0.99 (t, *J* = 7.4 Hz, 3 H) ppm.

Representative Procedure – Hydration of Oct-2-yne (7d), in which [D_8]Toluene was Used (Table 2, Entry 14): Compound **2·**AuCl (17 mg, 0.01 mmol) was added under argon to a solution of oct-2-yne (0.29 mL, 2.0 mmol) in toluene (1 mL) and H_2O (0.05 mL, 2.5 mmol). The mixture was stirred at room temperature for 5 min, AgOTf (3 mg, 0.012 mmol) was then added, and the whole system was immersed in a 50 °C preheated oil bath. After stirring for 1 h, the reaction mixture was allowed to cool to room temperature. Purification by short-plug silica-gel column chromatography with use of a Pasteur pipette and [D_8]toluene as eluent gave a colorless C_7D_8 solution. ^{1}H NMR spectroscopy determined that the product consisted of 88 % **9d** and 12 % **8d**. The ^{1}H NMR spectroscopic data for **9d** and **8d** were identical to those for commercially available authentic samples. The stack of those ^{1}H NMR spectra is shown in Figure S1 in the Supporting Information.

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

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[16] In the hydration reactions of **7c** and **7d**, the gold complexes **2**·AuCl, **5**·AuCl, and **6**·AuCl completed reactions and predominantly afforded ≈10:90 molar ratios of **8**:**9**; thus, there were not many differences in catalyst capabilities. On the other hand, alkynes **7g**, **7h**, and **7i** were not hydrated in the presence of **2**·AuCl, **5**·AuCl, or **6**·AuCl.
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