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Communication

Supramolecular Catalysts

Evaluation of the Reactivity of Metallocatalytic Cavities in the Dimerization of Terminal Alkynes

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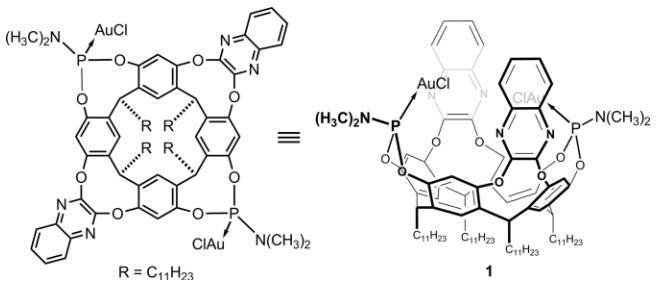
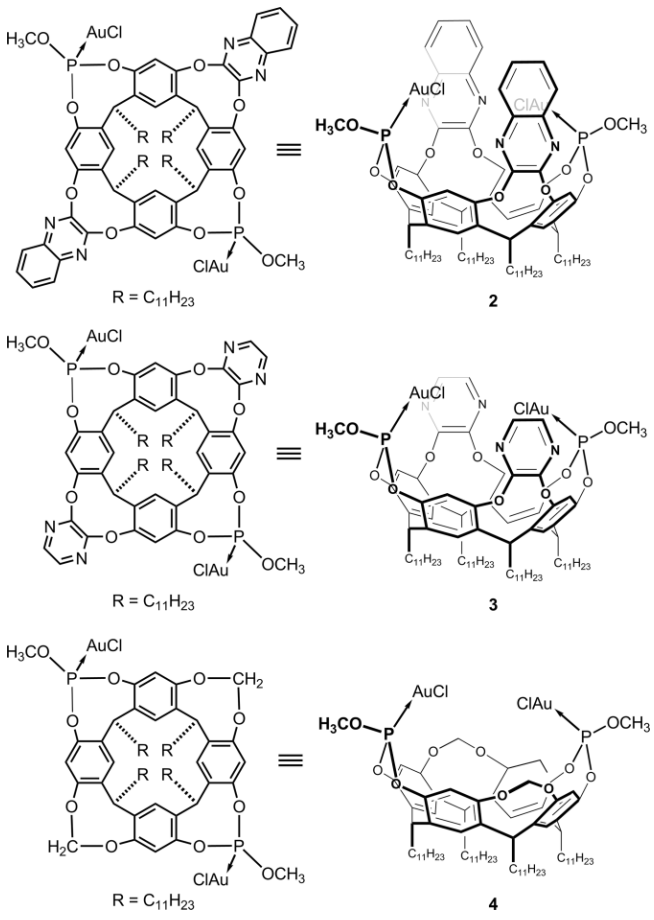
Abstract: The effect of a metallocatalytic cavity flanked by aromatic rings on the catalytic dimerization of terminal alkynes was explored through a comparison with model catalysts that weakened the cavity. The diquinoxaline-spanned resorcin[4]-arene provided a definite compartment, in which the two Au centers enticed two alkynes to undergo the coupling reaction. We synthesized two kinds of model compounds in which one lacked two quinoxaline walls and the other had two pyrazine walls and found that these catalysts exhibited much lower reactivity. The two quinoxaline moieties proved to be quintessential for the catalytic event.

Introduction

The development of introverted metal cavitands for catalytic use has attracted attention, because the enforced cavities allow enzymatic catalysis to be to mimicked.[1–3] Actually, for example, new metallocyclodextrins ligated with N-heterocyclic carbenes and monodentate phosphane were previously shown to elegantly catalyze cyclization and hydroformylation reactions.[4] On the other hand, our group recently synthesized introverted bis-Au cavitand **1** that was flanked by two quinoxaline walls and was based on resorcin[4]arene (Scheme 1); we found that the metal cavitand catalyzed the cross-dimerization of different terminal alkynes.[5] We already demonstrated control experiments in which an introverted mono-Au cavitand,[6] AuCl·PPh_3, and AuCl·$S(CH_3)_2$ had no catalytic activity; however, the effect of its cavity space surrounded by quinoxaline walls has not been verified, because the bis-Au model complex with two walls removed from **1** does not exist. We tried to synthesize this model, but the two fragile P–N bonds precluded its preparation in pure form.



Scheme 1. Introverted bis-Au phosphoramidite cavitand **1**.



Scheme 2. Introverted bis-Au phosphite cavitand **2** and corresponding models **3** and **4**.

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Herein, we present the synthesis of bis-Au complex **2** and corresponding models **3** and **4**, including a comparison of their reactivities in dimerization reactions (Scheme 2). In models **3** and **4**, for which the former equips the space with two pyrazine walls and the latter lacks two walls of its parent **2**, the two Au atoms are directed towards the appended resorcin[4]arene core. We anticipated that evaluation of the reactivities of **2**, **3**, and **4** in the previously reported dimerization reactions would unveil the role of the cavity enclosed by the two walls of **2** and the origin of the supramolecular catalysis.

Results and Discussion

The route for the synthesis of **2** is illustrated in Scheme 3. The reaction between tetraol platform **5**[7] and $P(OCH_3)_3$ gave two of the three possible isomers ("out-out", "in-out", and "in-in"). The two isomers were readily separated by silica-gel column chromatography and were confirmed to be "out-out" **6** (36 % yield) and "in-out" **7** (22 % yield).[8] In the ^1H NMR spectrum of **6**, there is one doublet located at δ = 3.97 ppm with $^3J_{PH}$ = 8.7 Hz that can be attributed to $POCH_3$; in the spectrum of **7**, there are two doublets positioned at δ = 3.98 ppm with $^3J_{PH}$ = 8.3 Hz and at δ = 3.10 ppm with $^3J_{PH}$ = 12.4 Hz attributed to the same $POCH_3$ protons (Figure 1, a, b). The upfield-shifted resonance of **7**, that is, the one at δ = 3.10 ppm, suggests that one of the OCH_3 groups experiences the anisotropic effects of the aromatic π clouds and is oriented inwardly; thus, the two P–O bonds of **6** are directed outwardly. In addition, the chemical shifts of the $POCH_3$ protons show good match with those of previously reported *mono*-$POCH_3$ groups that are inwardly and outwardly tethered to triquinoxaline-spanned resorcin[4]arene.[9] Thus, **6** successfully reacted with $AuCl{\cdot}S(CH_3)_2$ to give bis-Au complex **2** in 62 % yield.

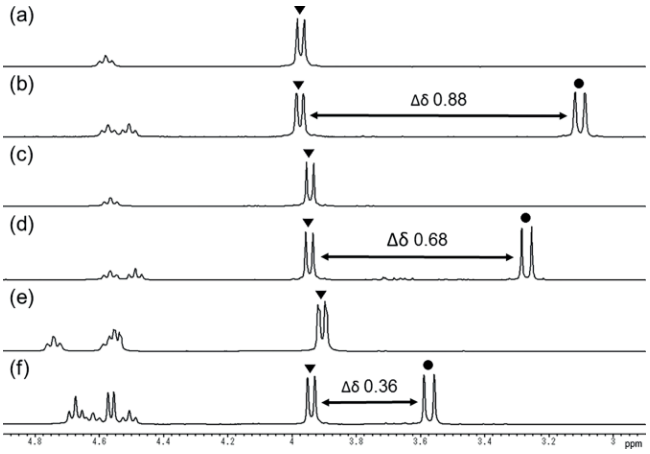
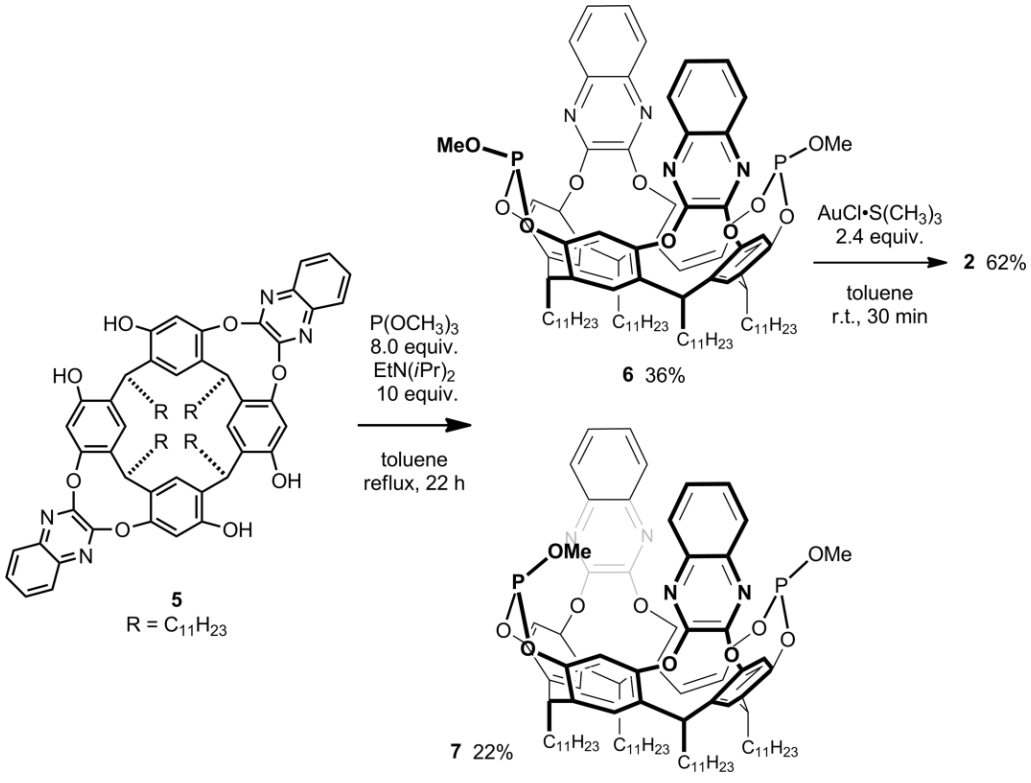
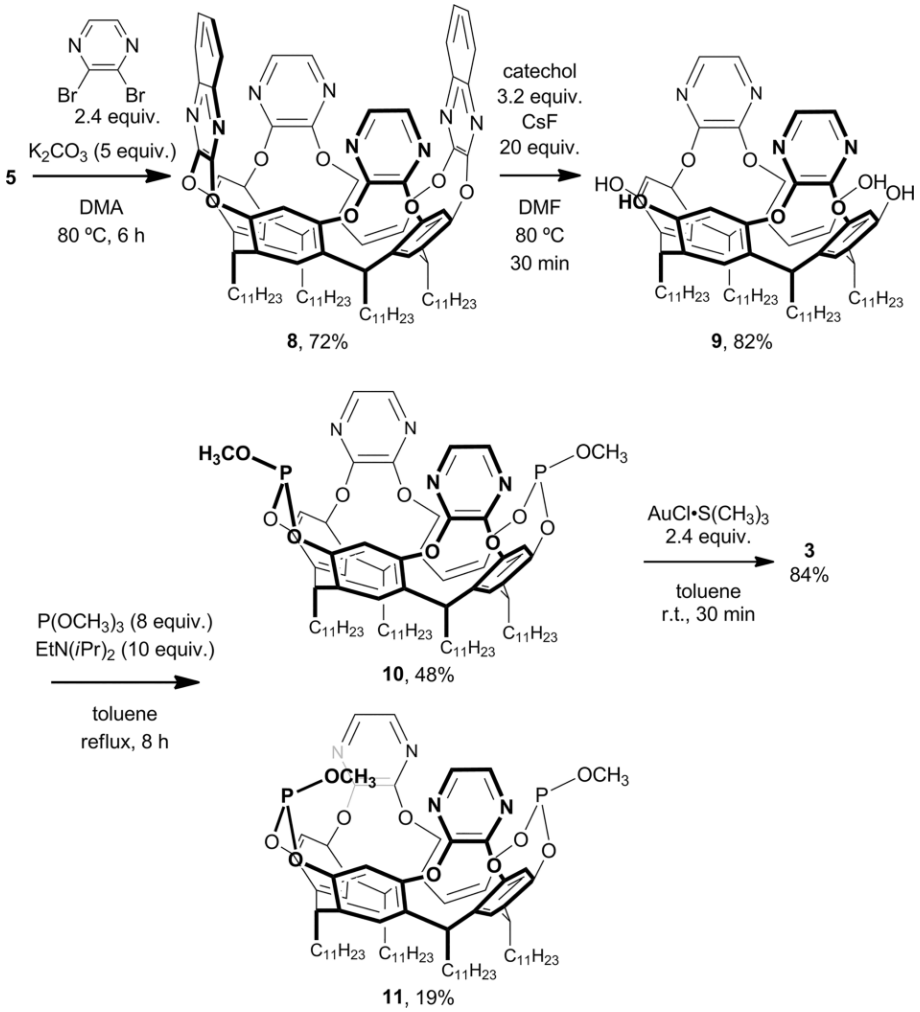


Figure 1. Portions of the ^1H NMR spectra of (a) **6**, (b) **7**, (c) **10**, (d) **11**, (e) **14**, and (f) **15** (400 MHz, $CDCl_3$). The peaks labelled with • and ▼ correspond to inward- and outward- oriented $POCH_3$ groups, respectively.

Then, dipyrazine-spanned resorcin[4]arene **3** was synthesized, as shown in Scheme 4. The platform reacted with 2,3-dibromopyrazine to give **8** in 72 % yield,[10] and the two quinoxaline walls of **8** were selectively removed in the presence of catechol and CsF in DMF solvent; thus, resultant dipyrazine-spanned **9** was successfully obtained in 82 % yield. The reaction between tetraol **9** and $P(OCH_3)_3$ also gave two of the three



Scheme 3. Synthesis of **2**, **6**, and **7** from tetraol platform **5**.

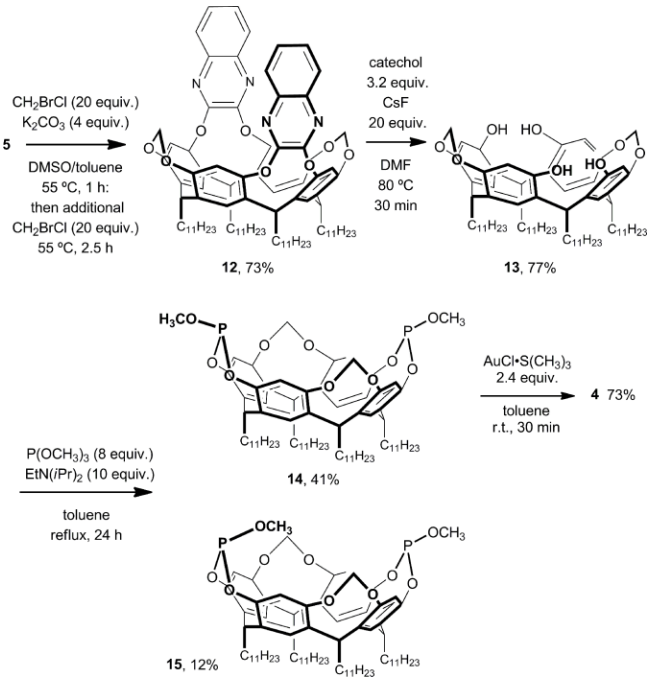


Scheme 4. Synthetic route to **3** through dipyrazine-spanned resorcin[4]arene **10**.

possible isomers: "out-out" **10** in 48 % yield and "in-out" **11** in 19 % yield. In the ^{1}H NMR spectrum of **10**, one doublet for the POCH_3 group is located at δ = 3.94 ppm with $^3J_{PH}$ = 9.0 Hz, and in the ^{1}H NMR spectrum of **11**, two doublets for the POCH_3 group are positioned at δ = 3.95 ppm with $^3J_{PH}$ = 8.9 Hz and at δ = 3.27 ppm with $^3J_{PH}$ = 12.4 Hz (Figure 1, c, d). The upfield shifted peak of **11**, that is, that one at δ = 3.27 ppm, suggests that one of the OCH_3 groups experiences the anisotropic effects of the π clouds of the resorcin[4]arene and pyrazines and is thus oriented inwardly; hence, the two P–O bonds of **10** are directed outwardly. Therefore, **10** reacted with $AuCl•S(CH_3)_3$ to give bis-Au complex **3** in 84 % yield.

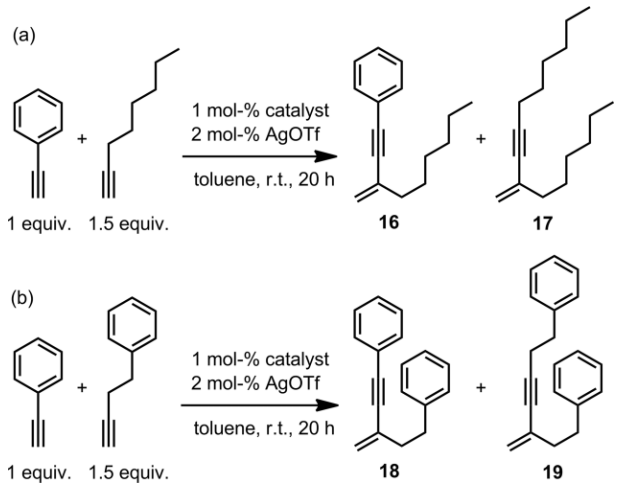
The stereodefined synthesis of model **3** is shown in Scheme 5. Starting **5** was bridged by reaction with CH_2BrCl under basic conditions to give **12** in 73 % yield.[11] The use of catechol and CsF in DMF at 80 °C resulted in the removal of two quinoxaline walls from **12** in 74 % yield. Similar to the synthesis of **6**/**7** and **10**/**11**, the reaction between tetraol **13** and $P(OCH_3)_3$ yielded two of the three possible isomers: "out-out" **14** in 41 % yield and "in-out" **15** in 12 % yield. In the ^{1}H NMR spectrum of **14**, one doublet for the POCH_3 group is located at δ = 3.92 ppm with $^3J_{PH}$ = 9.0 Hz, and in the ^{1}H NMR spectrum of **15**, two doublets for POCH_3 are positioned at δ = 3.94 ppm with $^3J_{PH}$ = 8.9 Hz and at δ = 3.58 ppm with $^3J_{PH}$ = 12.7 Hz (Figure 1e,f). Interestingly, the differences in the chemical shifts of the inward-pointing POCH_3 groups in **7**, **11**, and **15** are 0.88, 0.68, and 0.36, respectively (Figure 1, b, d, f): this is important evidence suggesting that the two quinoxaline walls create a definite compartment that is more heavily influenced by the π clouds than the compartments of the pyrazine-walled and methylene-bridged cavitands. Complexation between **14** and $AuCl•S(CH_3)_3$ proceeded, and purification by short-plugged column chromatography yielded desired model bis-Au **4** in 73 % yield.

The direct and selective dimerization reaction of terminal alkynes as a means to prepare enynes, without the requirement for any preactivation of the alkynes, is one of the most powerful reactions from the viewpoint of green chemistry.[12] Particularly, the design of a supramolecular approach capable of catalyzing the cross-dimerization reaction is of continuous interest, because it produces head-to-tail-fashioned enynes on the basis of molecular recognition as a rare event. Thus, the reactivities of



Scheme 5. Synthetic route to nonwalled **4** through methylene-bridged **14**.

supramolecular **2** and corresponding model **3** and **4** were first examined in the cross-dimerization of ethynylbenzene with two alkynes, namely, 1-octyne and 4-phenyl-1-butyne (Scheme 6).



Scheme 6. Cross-dimerization reactions of ethynylbenzene with (a) 1-octyne and (b) 4-phenyl-1-butyne.

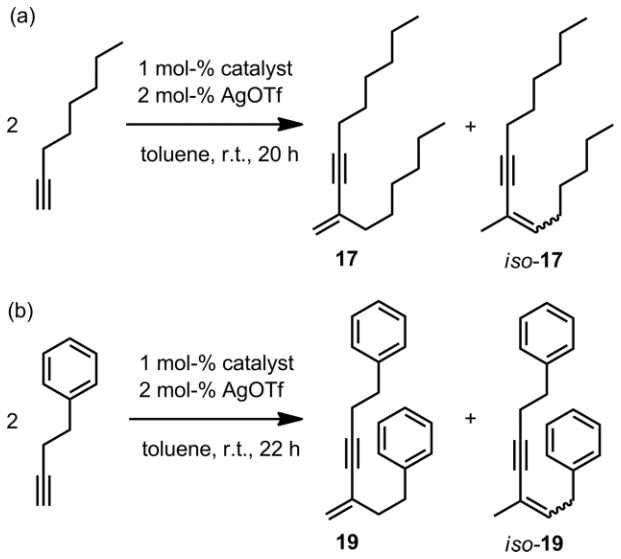
Reactions were performed in toluene at room temperature with a mixture of ethynylbenzene and the corresponding partner (1.5 equiv.) in the presence of the bis-Au catalyst (1 mol-%) and silver trifluoromethanesulfonate (AgOTf, 2 mol-%). Under these conditions, cross-adduct **16** or **18** and homoadduct **17** or **19** were the only products obtained, and the cross-adducts were predominantly formed. The molar ratios of cross-adducts to homoadducts and the yields of the isolated cross-adducts are summarized in Table 1. Bis-Au **2** catalyzed the reactions to provide yields of 57–58 % with molar ratios of cross-adducts to homoadducts of 3.0:1–3.1:1 (Table 1, entries 1 and 2). In contrast, pyrazine-type bis-Au **3** gave markedly lower yields of 6–9 % with molar ratios of cross-adducts to homoadducts of 4.3:1–3.0:1 (Table 1, entries 3 and 4). Surprisingly, model bis-Au **4** did not catalyze any reaction (Table 1, entries 5 and 6). For entries 3–6, most of the starting alkynes remained, and a ketone byproduct formed by hydration of 1-octyne or 4-phenyl-1-butyne was remarkably observed.[13]

Table 1. Cross-dimerization in the presence of catalysts **2**, **3**, and **4** according to Scheme 6.[a]

Entry	Catalyst	Alkyne	Yield[b] [%] of **16** or **18**	Molar ratio[c] **16**/**17** or **18**/**19**
1	**2**	1-octyne	58	3.0:1
2	**2**	4-phenyl-1-butyne	57	3.1:1
3	**3**	1-octyne	6[d]	4.3:1
4	**3**	4-phenyl-1-butyne	9[d]	3.0:1
5	**4**	1-octyne	0[d]	–
6	**4**	4-phenyl-1-butyne	0[d]	–

[a] Reaction conditions: ethynylbenzene (102 mg, 1 mmol), alkyne (1.5 mmol), bis-Au catalyst (0.01 mmol), AgOTf (5 mg, 0.02 mmol), toluene (5 mL). [b] Yield of isolated product. [c] Determined by analysis of the crude material by ^{1}H NMR spectroscopy. [d] Starting alkyne remained, and the production of a ketone was observed.

Given the efficiency of the two quinoxaline walls in **2**, we then investigated the homodimerization reactions of 1-octyne and 4-phenyl-1-butyne in the presence of **2**, **3**, and **4** (Scheme 7). Under the conditions outlined in Scheme 7, catalyst **1** mainly yielded an *exo*-methylene compound (i.e., **17** or **19**):[5] depending on the starting alkyne, the product included the corresponding isomer with an internal olefin (i.e., *iso*-**17** or *iso*-**19**).[14] The results obtained with the use of **2**–**4** as catalysts are summarized in Table 2. Bis-Au **2** resulted in the predominant formation of *exo*-methylenes **17** and **19** in yields of 63–65 % (Table 2, entries 1 and 2). In contrast, pyrazine-type **3** gave markedly decreased yields of 14–18 %, and *iso*-**17** and *iso*-**19** were formed in noticeable amounts (Table 2, entries 3 and 4). With the use of nonwalled catalyst **4**, trace amounts of the cou-



Scheme 7. Homodimerization reactions of (a) 1-octyne and (b) 4-phenyl-1-butyne.

pling adducts were observed (Table 2, entries 5 and 6). For entries 3–6, there were a lot of unreacted alkynes and 2-octanone or 4-phenylbutan-2-one in their crude states.[13] From the results of Tables 1 and 2, the superiority of **2** over **3** and **4** is clear, particularly in the terms of the chemical yields. The pyrazine walls surely provide some degree of catalytic reactivity relative to nonwalled **4**; however, it is not effective at all. Thus, comparison between **2** and **3** unveiled that the quinoxaline substructure in **2** plays a quintessential role in the supramolecular catalysis.

Table 2. Homodimerization in the presence of catalysts **2**, **3**, and **4** according to Scheme 7.[a]

Entry	Catalyst	Alkyne	Yield[b] [%] of **17** or **19**	Molar ratio[c] **17**/*iso*-**17** or **19**/*iso*-**19**
1	**2**	1-octyne	63	≈100:0
2	**2**	4-phenyl-1-butyne	65	96:4
3[d]	**3**	1-octyne	18	97:3
4[d]	**3**	4-phenyl-1-butyne	14	88:12
5	**4**	1-octyne	trace[d]	>99:1
6	**4**	4-phenyl-1-butyne	trace[d]	>99:1

[a] Reaction conditions: alkyne (1 mmol), bis-Au catalyst (0.01 mmol), AgOTf (5 mg, 0.02 mmol), toluene (5 mL). [b] Yield of isolated product. [c] Determined by analysis of the crude material by ^{1}H NMR spectroscopy. [d] Starting alkynes remained, and the production of a ketone was observed.

To compare more accurately the catalytic activities of **2**–**4**, we recorded the chemical yields and molar ratios of **19**/*iso*-**19** by varying the temperature in the homodimerization of 4-phenyl-1-butyne (Table 3).[5] The reaction temperature was increased from room temperature to 110 °C. Upon using **2**, increasing the temperature resulted in full consumption of the starting alkyne within 2 h (Table 3, entries 1–3). Interestingly, the molar ratios of **19**/*iso*-**19** became almost completely inverted from ca. 96:4 to 2:98.[15] Upon using **3**, increasing the temperature did not increase the rate of the reaction and the chemical yields remained low (Table 3, entries 4–6). The molar ratio of **19**/*iso*-**19** at 75 °C was reversed to 16:84 compared to 88:12 at room temperature (Table 3, entry 5); this is in contrast to that observed for catalyst **2**. Upon using nonwalled **4**, the amount of *iso*-**19** formed increased as the temperature was increased, but the yields were still terribly low (Table 3, entries 7–9). The molar ratio of **19**/*iso*-**19** = 51:49 obtained at 110 °C with the use of catalyst **4** was remarkably neutral (Table 3, entry 9), compared to the ratio of 2:98 obtained with the use of catalyst **2** (Table 3, entry 3) and the ratio of 6:94 obtained with catalyst **3** (Table 3, entry 6). Thus, two main points can be drawn from Table 3. First, the presence of both quinoxaline and pyrazine walls strongly affects the product selectivity of the isomeric ratios, which are remarkable at high temperatures. Second, the structural difference between the quinoxaline and pyrazine walls significantly enhances the consumption of starting 4-phenyl-1-butyne at 75 and 110 °C.

Table 3. Temperature-dependent ratios of **19**/*iso*-**19** according to Scheme 7 (b).

Entry	Catalyst	Temp. [°C]	Time [h]	Yield[a] [%]	Molar ratio[b] **19**/*iso*-**19**
1	**2**	r.t.	20	65	94:6
2	**2**	75	2	67	48:52
3	**2**	110	2	40	2:98
4[c]	**3**	r.t.	22[d]	14	88:12
5[c]	**3**	75	22[d]	28	16:84
6[c]	**3**	110	16[d]	11	6:94
7[c]	**4**	r.t.	18[d]	trace	>99:1
8[c]	**4**	75	18[d]	18	95:5
9[c]	**4**	110	18[d]	12	51:49

[a] Yield of isolated mixture **19**/*iso*-**19**. [b] Determined by ^{1}H NMR spectroscopy. [c] A large amount of byproduct 4-phenylbutan-2-one was formed. [d] Unreacted 4-phenyl-1-butyne remained in the crude state.

Conclusion

In summary, we found that the cavity space of **2** flanked with two quinoxaline walls was indispensable for the catalytic dimerization of terminal alkynes. Particularly, the two-quinoxaline substructure plays an important role in this supramolecular catalysis. The results suggest that the two quinoxaline walls provide three salient features: One, the quinoxaline parts significantly force the interior space of **2** into a stronger π-cloud environment than that found in the interior spaces of **3** and **4**. Two, the quinoxaline-created cavity drastically enhances interaction of the two alkyne partners, and this is decisively influenced by the structural differences between the quinoxaline and pyrazine moieties. Three, the quinoxaline walls impact the product selectivities as compared to the nonwalled cavitand, and their effects are somewhat similar to those of the pyrazines walls. These three features strongly inter-relate the origin of the catalytic effect. The effect would be complemented by stabilization of reactive intermediates and chemical processes, which are consequences inherent to such a limited space.[16–18] The large reactive sites in **3** and **4** allow various transition-state geometries, whereas the confined space in **2** limits the transition states and the desired reactive species may be actively stabilized.[19–21] In addition, from the viewpoint of mechanistic insight, the expanded π-orbital space of **2** could delocalize electrons that interchange between the two alkynes during the course of the reaction; thus, the cavity stabilizes the process and reduces the enthalpic price of the reaction. Clearly, this result will constitute an illustration of the high potential of introverted bis-metal cavitands in homogeneous catalysis. Our progress reported herein about the cavity space is the first decisive evidence showing the catalytic utility of quinoxaline-spanned resorcin[4]arene, which is a monumental platform in supramolecular chemistry.[22] This result should serve as an intellectual basis for future catalytic cavitand chemistry. There are many more variations of metals and reactions to try. In these endeavors, we look forward to reporting on the supramolecular advantages of this easily accessed chemical cavitand platform.

Acknowledgments

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Keywords: Supramolecular chemistry · Cavitands · Macrocycles · Encaged catalysts · Alkynes · Gold · P ligands

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[13] For entries 1 and 2 in Tables 1 and 2, unreacted substrates remained in the crude states, and a minor amount of a ketone byproduct was observed.
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