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COMMUNICATION

Au-Cavitand Catalyzed Alkyne-acid Cyclizations

Tam D. Ho and Michael P. Schramm *[a]

Dedication: To Julius, in appreciation of your mentorship, on the occasion of your birthday – this one's for you.

Abstract: Supramolecular cavitands that contain inwardly directed functional groups have yielded specialized transformations and trapping of reactive intermediates. A recently reported 3-wall Au cavitand provides exciting opportunities for supramolecular catalysis. In this study, a variety of substituted γ-alkynoic acids were reacted to give lactones. The interaction of peripheral "R" groups revealed differential catalyst behavior. Extremely large and small groups reacted with appreciable rate. Intermediate sized groups however, slowed significantly: giving support that size-specific binding is at play when using cavitands as a scaffold for gold catalysis. These results serve as some of the first evidence of the interplay between substrate and cavitand interior in the catalytic sphere.

Introduction

Natural receptors and enzymes have a variety of features that have attracted attention from many areas of the chemical community. Supramolecular chemists in particular draw multifaceted inspiration from these entities. The first salient feature is a well-defined internal space, often hydrophobic in nature, and ultimately suitable for a specialized guest molecule. Paradigms for recognition of guests emerged from biological archetypes: 1) Fischer's lock and key[1] and 2) Koshland's induced fit.[2] Synthetic receptors have taken the forms of cages and vases of a variety of sizes, shapes and functions. We know some of them as "cavitands,"[3] "cryptands," "carcerands," and "capsules"[4] (to name a few of the ones that start with the letter c!). Logically nature provides one set of rules for all hosts and synthetic ones have afforded direct observation of physical chemical phenomenon by techniques like NMR that can relate either forward from or backward towards their natural counterparts. The second important feature of enzymes that inspire us is that they perform numerous specialized chemical transformations.

Resorcinarene cavitands have steadily been explored as a relevant synthetic platform to explore the possibilities of catalysis. The first antecedents employed Kemp's triacid and successfully placed a carboxylic acid "inwardly directed." The bound lifetime of amines increased[5] and the racemization of a chiral amine was stopped.[6] A further variation used an inwardly directed aldehyde to directly observe an otherwise labile hemiaminol intermediate.[7,] Organocatalysis was achieved using an inwardly directed acid that cyclized 5-hydroxy-pent-1-eneoxides, 100-fold rate enhancements as well as selective 5-exo products were formed.[9] We find two reports with metals particularly inspiring. A cavitand outfitted with palladium catalyzed allylic alkylation reactions[10] and catalysis of choline to acetyl choline was predicated on choline binding inside a cavitand adjacent to a Zn–salen wall.[11] A much earlier report installed four AuCl centers onto a shallower resorcinarene that had bridging phosphonito groups.[12]

More recently and much more broadly supramolecular science has taken many common themes and explored ways to study catalysis. One approach has been to use very bulky phosphine "end caps" to coordinate to Au•triflamide. The resulting catalyst has hole-like topology and displays very special reactivity compared to electronically similar, albeit smaller ligands (incapable of providing a hole/pocket).[13] There are other ways to provide reactants holes to find metal centers buried in, cyclodextrins with a proximal NHC ligand have provided a platform to install Cu, Ag and Au. Regioselective hydroboration depends on CD size and more deeply a change in mechanism.[14] Gold on the other hand could affect enyne cyclization, including examples where the CD pocket gave ee.[15] Another approach has taken supramolecular structures and non-covalently included a reactive center via host-guest principles. A tetrahedral assembly of six bisbidentate ligands and four Ga centers provided an enticing environment for Me_3PAuCl, which then catalyzed intramolecular hydroalkoxylation of allenes.[16] Returning to resorcinarene, the remarkable self-assembly of six units provides a very large environment within which to work.[17] NHC-Au catalysts provide relevant points to consider, as their catalytic activity drastically changes inside the hexamer.[18-20] These themes have been more carefully elaborated on in a series of recent reviews.[21-24]

Returning to this contribution, the "inwardly directed phosphorous" 3-walled cavitand **1** plays significant role (Scheme 1).[25] **1** afforded complexation with Au-Cl, placing a gold metal center directly inside the aromatic walls of a well-defined and characterized (by x-ray) binding pocket.[26] Catalysis screening ensued with **2**; both hydration of alkynes as well as Conia-ene reactions were performed. These first modest reports demonstrated some potential for general cavitand catalysis. The role of the cavitand itself remains open for exploration. 2-wall bis-gold cavitands[27-29] and 2-wall mono-gold mono-phosphorous oxide cavitands[30, 31] followed quickly and these species point to a role of intermediate stabilization as well as the importance of correct spatial-positioning. They have been added to a very recent review that encompasses earlier mentioned topics as well as the most recent approaches (e.g. using $M^{12}L^{24}$ cages).[32]

Herein we report that new opportunities for the three-wall variation, **2** continue to emerge. We report that γ-alkynoic acids with a variety of R groups behave differently than each other, but do not follow the fundamental principles of sterics that we are used to (e.g. large is slow, small is fast). Instead, when the cavitand acts

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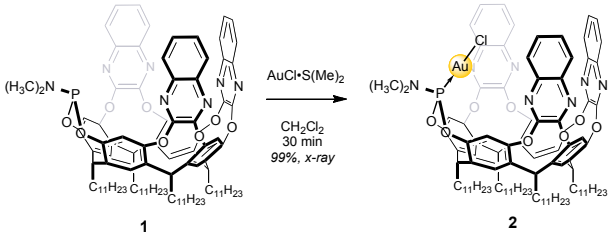
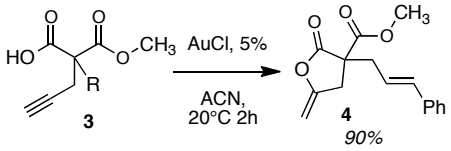
as the catalyst, R group size matters most likely related to host-guest chemistry. Guests that contain specific molecular fragments, ones that have previously been demonstrated to be good guests for 4-wall cavitands (e.g. benzyl sized) slowed reactions. This happens when they decorate the periphery of an otherwise suitable substrate. Small (e.g. propargyl) and large (e.g. octyl, napthyl, 3,5-dimethylbenzyl) R-groups, behave similarly to one another, without slowing.



Scheme 1. 3-wall resorcin[4]arene cavitands: Inwardly directed Phosphorous **1** and Gold-Cl **2**.

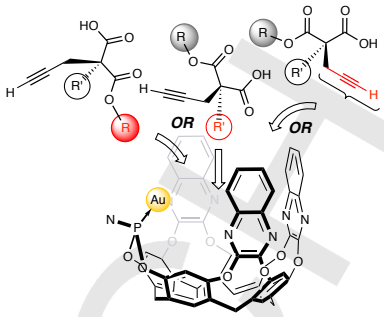
Results and Discussion

The gold catalyzed cyclization of γ-alkynoic acids has been previously reported (Scheme 2).[33] A variety of R groups on methylester-acid-alkyne **3** were well tolerated at room temperature with 5 mol% of AuCl (9 examples, 75-97% conversion). Product **4** is typical, and improvements to this work are ongoing.[34]



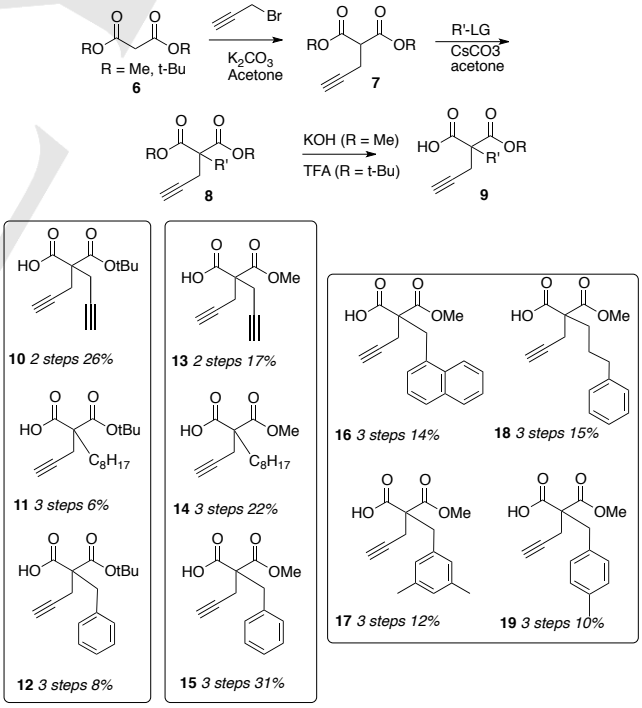
Scheme 2. "Au(I)-Catalyzed exo-Selective Cycloisomerization of Acetylenic Acids."[33]

The straightforward preparation of mono-acid alkynes **3** and our 3-walled Au cavitand **2** led us to consider the effect of spectator "R" groups on reactivity. Could flanking "R" groups play a role in recognition that translates into a change in rate of cyclization? Scheme 3 illustrates a generic substrate **5**, were we note two points of variation, R and R'. If the cavitand prefers either spectator or the alkyne, does it alter the outcome? We prepared several substrates with the hopes of uncovering variables that result in differential outcome based on host-guest chemistry principles. We wondered if the alkyne is always the most kinetically accessible? If so then R and R' should play no role. Conversely would a R or R' recognition event speed up, slow or stop a reaction?



Scheme 3. Potential modes of host-guest recognition.

Scheme 4 outlines the requisite procedures for a small library of compounds (for full details see Supporting information). In short, malonates were either mono or dialkylated with propargyl bromide. In the case of monoalkylation, a second group was installed in a subsequent step. Statistical ester removal was performed using KOH when R = Me and TFA when R = tBu. All compounds were characterized by NMR spectroscopy and rigorously purified before being subject to catalytic screening. t-Butyl ester alkyne-acids with dipropargyl (**10**), n-octyl (**11**) and benzyl (**12**) R'-groups were prepared. Methyl analogs to dipropargyl (**13**), n-octyl (**14**) and benzyl (**15**) were prepared. A subset of substrates **16-19** were prepared after initial screening of **10-15**.



Scheme 4. Preparation of substitude alkyne-acids and collection of substrates for screening. t-Butyl alkyne-acids, **10-12** and Methyl alkyne-acids **13-18**, with three step isolated yields (full details in ESI).

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Owing to limited solubility of cavitand **2** in acetonitrile, we conducted a first round of catalyst screening in Chloroform and Toluene at 23 and 70 °C. Percent conversion was calculated by integration of ^{1}H NMR; only starting material and product peaks were observed in the transformation of terminal alkyne to lactone (see Scheme 2). 23 °C proved to be too slow for practical use, no substrates were completely converted to lactone after 48 hours in the presence of 4 mol% **2**: **13** (63%), **14** (47%) and **15** (21%). At 70 °C the reactions were fast enough to monitor over a 24-hour period and ultimately provided a means to identify differences (Table 1). Other additives are known to accelerate these reactions, which we will discuss in a future paper. Table 1 illustrates the results of this initial screening at 70 °C. Reactions of substrate **13** containing two propargyl groups was very efficient, coming to completion after 4 hours. When R' = n-octyl (**14**) an additional 20 hours was required. The dipropargyl substrate **13** likely has more efficient conversion than **14** owing to an additional reactive alkyne center being present. When R' = benzyl (**15**) the reactions were markedly slower than **14**. Especially at later time points (e.g. 4, 24 hr). For the uninitiated reader, benzyl is a known guest for resorcinarene cavitands and in non-completive solvents can be observed inside by NMR.

Table 1. First Screen: Effect of Solvent, side chain R' and ester R on the cyclization of alkyne-acids **10-15** (0.12 M) with gold cavitand **2** (4 mol%). **Bold** entries indicate effective reaction completion time point, beyond which little conversion was observed.

Substrate R= Me, R' =	Time	$CDCl_3$	Toluene-d_8	**Substrate** R= t-butyl, R' =	$CDCl_3$
		70 °C	70 °C		70 °C
13 Dipropargyl	1 hr	63%	50%	**10** Dipropargyl	24%
	2 hr	84%	69%		36%
	4 hr	**99%**	**98%**		64%
	24 hr				**96%**
14 n-octyl	1 hr	28%	20%	**11** n-octyl	60%
	2 hr	46%	37%		69%
	4 hr	92%	70%		**77%**
	24 hr	**94%**	**96%**		77%
15 benzyl	1 hr	20%	17%	**12** benzyl	23%
	2 hr	35%	20%		31%
	4 hr	58%	24%		**52%**
	24 hr	**67%**	**81%**		53%

Within Table 1 we also compare the effect of the t-butyl ester group. We note a slowing of conversion compared to the smaller methyl R group. The bulkier ester group could play one of two plausible roles in the decreased rate of reaction. Either it is simply larger (**10-12**) than methyl (**13-15**) and prevents the alkyne from accessing the Au cavitand **2**, or the t-butyl group has some direct interaction with the cavitand interior that the methyl group does not. These scenarios could alter the time or orientation that the alkyne group has with the Au center and thus reactivity slows. We leave this point unresolved, as a more compelling series of results emerges when we look at R'.

The benzyl group found in **12** and **15** has more steric bulk than the dipropragyl (**10** and **13**), but isn't n-octyl (**14**, **11**) as cumbersome as benzyl? To explore if this was simply a steric effect where bulk prevents the alkyne from finding gold we prepared a second generation of substrates that vary the size of the aromatic R' group with respect to **15**. As illustrated in Scheme 4, R' = 1-naphthyl **16**, 3,5-dimethylbenzyl **17** and propenylbenzene **18** were prepared. If steric repulsion is the primary director, then these substituents should be equally slow to **15**, if not *more so*. Of note to the reader is that substituted naphthyls as well as xylene-like or mesitylene-like substrates are not particularly good guests for resorcinarene cavitands. Their girth prevents effective entrance into the cavitand, this led early pioneers in the field to use mesitylene-d_{12} as an NMR solvent, so as to exclude it from competing with guests for cavitand[3] and capsule interiors.[35] Indeed chloroform, benzene, and para-disubstituded aromatics have been extensively studied in resorcinarene capsules, where they can be directly observed to habitate.[36, 37]

Table 2 shows the results of these benzyl analogs in 3 different solvents at 70 °C. First examination in chloroform reveals that 1-naphthyl and 3,5-dimentyl benzyl are *faster* than benzyl, while the longer benzyl variant, namely propenylbenzene was slower.

Toluene is a suitable guest for cavitand interiors and when it was used as the reaction solvent, napthyl **16** and 3,5-dimethylbenzyl **17** are the fastest, benzyl **15** and propenylbenzene **18** are slower, but all are similar (74-100% after 24 h). Finally, in mesitylene – a solvent that can't appreciably occupy the cavitand we see the largest guests continue to convert the fastest but this time there is an inversion for the slowest, benzyl **15** wins. The observation that the largest substituents react with similar profiles in different solvents supports the idea that they do not fit inside and thus the reactive centers are free to react. When the side-chain is suspected to fit inside, the reactivity slows in a variety of solvents, more so in non-competing solvents.

Table 2. Effect of side chain R' size with larger aromatics on the cyclization of alkyne-acids **15-18** (0.12M), 70 °C, in Chloroform, Toluene and Mesitylene, with 4% of gold cavitand **2**. Entires from Table 1 for ease of comparison are noted,[a] **bold** entries indicate effective reaction endpoint.

Substrate R = Me, R' =	Time	$CDCl_3$	Toluene-d_8	Mesitylene-d_{12}
15 benzyl	1 hr	20%[a]	17%[a]	5%
	2 hr	35%[a]	20%[a]	6%
	4 hr	58%[a]	24%[a]	7%
	24 hr	**67%[a]**	**81%[a]**	**39%** *slowest*
16 1-naphthyl	1 hr	27%	31%	28%
	2 hr	37%	45%	41%
	4 hr	58%	71%	76%
	24 hr	**81%**	**100%** *fastest*	**99%** *fastest*
17 3,5-dimethylbenzyl	1 hr	22%	23%	19%
	2 hr	30%	32%	57%
	4 hr	55%	56%	74%
	24 hr	**83%** *fastest*	**95%**	**87%**
18 propenyl benzene	1 hr	20%	17%	22%
	2 hr	28%	20%	27%
	4 hr	32%	25%	34%
	24 hr	**36%** *slowest*	**74%** *slowest*	**66%**

To further elucidate the role structure vs. reactivity as well as we conducted a series of detailed kinetics experiments. Substrates **15-18** and a previously unstudied p-methyl benzyl **19** were dissolved (0.12M) in $CDCl_3$ in the presence of 4 mol% of **2**. Samples were mixed and inserted (at t=120 s) into a pre-warmed (328.2K) NMR. The instrument was shimmed twice as the sample equilibrated and after 300 seconds of heating 30-35 spectra were acquired at nonlinear intervals over 24 hrs. The data was processed carefully and plots of concentration vs. time were generated. The data was fit to a 3-parameter exponential function (equation 1), after first trying many others.[38]

$$y = ae^{bx} + c \qquad \text{(equation 1)}$$

This function gives *b* as the exponential component and *c* is an offset that can take on many possible variables including instrumental artifacts, miscalibration, or as written this function can be applied to first order decay of a reactant as it approaches equilibrium (equation 2). At first glance this is an oversimplification, but the initial results already point to differential binding events which may or may not include equilibration.

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} P \qquad \text{(equation 2)}$$

Given many possible kinetic treatments,[39, 40] we first assumed that substrate *A* would behave under pseudo 1st order conditions, as the catalyst concentration is both low (4.0 mol %) and constant (at the end of the reaction the NMR of **2** is unchanged and characterizable with ~4 pulses). Equation 3 provides the usual representation of this assumption, where *I* represents a reversibly formed intermediate (in this case a host-guest complex), that irreversibly goes to product *P*.

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} I \xrightarrow{k_2} P \qquad \text{(equation 3)}$$

Applying the steady state approximation, such that the change in [I] with time = 0, and that under the current reaction conditions, product formation is irreversible (i.e. $k_{-2} = 0$, equation 3), the rate equation can take the simplified form (equation 4).

$$Rate = \frac{-d[A]}{-dt} = k_{obs}[A] \qquad \text{(equation 4)}$$

Where k_{obs} encompasses [cat], k_1, k_{-1}, and k_2. Based on our initial conversion data (Table 1 and Table 2), when we collected much more detailed "real-time" integral data many expected variations were observed (Table 3) (See ESI for NMR conditions, raw data and curve fits).

Table 3. Kinetic Analysis: Alkyne-acids (0.12 M) and gold cavitand **2** (4 mol%) were mixed in chloroform and monitored over 24 hours at 55 °C. k_{obs} reported in s^{-1}, r Error as the root mean square between the fit and raw data and Turn Over Number at the end of reaction (24 h).

Substrate	k_{obs} (s^{-1})	r Error	TON
1-napthyl (**16**)	8.56E-05	8.09E-07	21.4
dimethylbenzyl (**17**)	2.54E-05	4.33E-07	23.9
p-Methylbenzyl (**19**)	2.24E-05	7.60E-07	24.5
Propenylbenzene (**18**)	8.87E-05	2.86E-06	13.0
Benzyl (**15**)	5.59E-05	9.69E-07	*17.7*

First, substrates **16**, **17** and **19** all approach completion (21.4-24.5 TON, theoretical max = 25), but at different rates. This was obvious visually from the raw data. Benzyl **15** has an observed rate constant between **16** and **17** but the reaction has disappointing turn over (17.7). Finally, propenylbenzene **18** mimics the rapid decline of substrate concentration similar to napthyl **16**, reflected in k_{obs}, but the turnover is much lower (13.0 vs 21.4).

This data reinforces our initial findings in Tables 1 and 2, R' groups are playing a significant role in how the reactive functional groups are allowed to interact with the catalyst. **19** was anticipated to behave like **15** and **18**, as toluene is a known guest for resorcinarene cavitands, we expected marked slowing of the

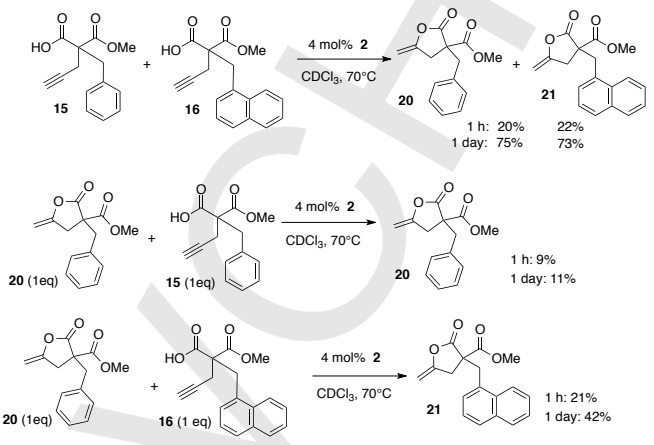
lactonization. But when we carried out the study this shape behaved similarly to dimethylbenzyl **17** which can not fit inside a cavitand. At this stage we applied a more recently developed series of kinetic tools. Reaction Progress Kinetic Analysis (RPKA)[41, 42] and Visual Kinetic Analysis[43, 44]. RPKA has been deployed successfully to resolve many kinetic issues including determining order of substrate, order of catalyst, catalyst decomposition and catalyst inhibition.[45, 46] Using RPKA we confirmed the k_{obs} reported in Table 3, taking the derivative of the 3-parameter exponential function and plotting against substrate concentration gave a straight line in each case, matching the k_{obs} with R^2 values of 0.989-1.0 (see ESI). We next repeated the kinetic analysis of **15** at 0.09 M and 0.06M concentrations. When we used time shifted Visual Kinetic Analysis we did not observe curve overlap especially when comparing 0.12M vs. 0.06M. If we had observed overlap then we can infer no product inhibition and no catalyst deactivation. This initial observation points to one of these possibilities. The same information can be retrieved by plotting the first derivative vs [A] (RPKA). We found that k_{obs} increased and TON decreasing with decreasing substrate concentration (Table 4). Again these results point to either product inhibition or catalyst deactivation. We believe these results also could be the result of substrate inhibition, which RPKA hasn't addressed to our knowledge as "same excess" experiments require two reactants to carry out. As both reaction partners exist in our substrates, the same excess experiment can't be performed precisely as prescribed.

Table 4. Kinetic Analysis: Alkyne-acid **15** (0.12, 0.09, 0.06 M) and gold cavitand **2** (0.0048 M) were mixed in chloroform and monitored for up to 24 hours at 55 °C. k_{obs} reported in s^{-1}, r Error as the root mean square between the fit and raw data and Turn Over Number at the end of reaction (24 h). [a]Repeated from Table 3.

Substrate	k_{obs} (s^{-1})	r Error	TON
0.12 M **15**[a]	5.59E-05 [a]	9.69E-07 [a]	*17.7* [a]
0.09 M **15**	5.86E-05	1.69E-06	11.5
0.06 M **15**	6.50E-05	2.19E-06	7.7

The increasing k_{obs} as well as non-overlapping time shifted kinetic traces can be evidence for either catalyst degradation or product inhibition. Catalyst degradation seems unlikely in this case: A) the catalyst can complete 24.5 out of 25 cycles with other substrates (Table 3), B) the catalyst remains unchanged by ^{1}H NMR analysis at the end of the cycle, C) no conceivable covalent modification of catalyst exists.

Finally, we did a series of initial competition experiments to probe why **15** displays significantly slower kinetics (Scheme 5). First, we directly compared **15** and **16** by mixing them together and subjecting them to 4 mol % **2**. We immediately noted that the rates of these two substrates seemed to mimic each other at the 1 hour time point and were similar after 24 hours. These were similar to the non-competition results (Table 2). Unsatisfied, we prepared the lactone **20**, the cyclization product **15** and then doped reactions of substrate **15** and **16.** Upon reaction with **2**, a stark decrease in conversion was noted. After 24 hours, only 11% of substrate **15** was converted into **20** (typically 67%, Table 2). Next, with competition partner **16** a deceleration of reaction was again observed. After 24 hours only 42% of the substrate was converted into lactone **20** (typically 81%, Table 2). These results support a possibility that lactone **20** is an inhibitor for catalyst **2**.



Scheme 5. Direct competition of **15** and **16** and reaction doping with lactone **20**. Conversion % is reported from ^{1}H NMR integration, all 4 species had cleanly resolved peaks. Conversion is reported per substrate and is = (product area / (product area + substrate area). Product/substrate competition of **20** with **15:** conversion % is reported from ^{1}H NMR integration of *additionally* formed product originating from **15**. Product/substrate competition of **20** with **16**, conversion is reported as **16** become **21**.

Conclusions

We have demonstrated that Au-cavitands possess catalytic ability in the cyclization of γ-alkynoic acids. Unlike prior published results with traditional AuCl catalysts, Cavitand **2** interacts with "spectator" groups. When t-butyl esters were compared to methyl ester analogs, there was a decrease in conversion, which we haven't fully explored. Work also remains to confirm the exact role of solvent as several different competitions could exist depending on substrate and product. Benzyl and propenylbenzene groups, despite their moderate size, slowed reactivity when compared to larger groups and a detailed kinetic analysis reveals information about both rate and TON. At decreasing concentrations of **15,** k_{obs} increases and when product **20** is used to spike reactions, evidence of inhibition exists. The product is capable of inhibiting the catalyst based on R' group and perhaps too this R' group results in substrate inhibition at high substrate concentration. To deeper understand this picture we recognize a broader rate equation will be necessary that will allow us to explore both the role of substrate and product binding with catalyst **2** (Equation 5).

$$A + cat \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [A\bullet cat] \xrightarrow{k_2} [P\bullet cat] \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} P$$

(equation 5)

Gold catalysis already is an intricate process when intramolecular reactions are involved, indeed activation of alkyne, ring closing, deprotonation and protonation of gold must occur.[47] In addition to a broader exploration of substrate and product concentrations to

get a better kinetic picture, detailed binding studies also await both us and the reader in a sequel.

Experimental Section

The electronic support information contains all procedures for the synthesis of new compounds including NMR characterization. Representative 4-time point stack plots from which tables 1 and 2 were constructed are included, as well as raw, fitted and derivative kinetic data used in tables 3 and 4.

Acknowledgments

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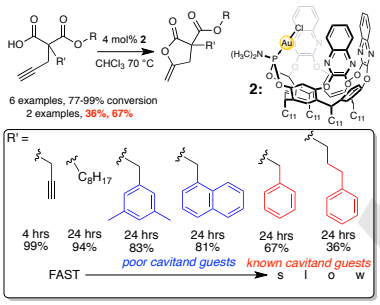
COMMUNICATION

Au-Cavitands place a reactive metal center inwardly directed to a well-studied binding pocket. The metal center retains its reactivity, what role does the pocket play? Specific sized groups that are known guests for cavitands slow the reaction progress of the lactonization of alkynoic acids. Initial kinetic treatment hints of substrate and product inhibition for select R groups.



Supramolecular Catalysis*

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