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# Gold-catalyzed Cycloisomerization Reactions within Guanidinium $M_{12}L_{24}$ Nanospheres: the Effect of Local Concentrations

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Gold-catalyzed cycloisomerization reactions have been explored using guanidinium functionalized  $M_{12}L_{24}$  nanospheres that strongly encapsulate gold complexes functionalized with a sulfonate group through hydrogen bonds. As the  $M_{12}L_{24}$  nanospheres can bind up to 24 gold complexes, the effect of local catalyst concentration on the reaction outcome can be easily evaluated. Also, the guanidinium groups of the sphere can weakly interact with the carboxylic group of the substrates, facilitating the pre-organization of the substrate near to the

catalytic active site. Both effects can influence the selectivity and rate of the gold-catalyzed transformation. Challenging acetate-containing substrates with internal acetylene functional groups can be cyclized efficiently within the  $M_{12}L_{24}$  nanospheres, where the pre-organization of the substrate plays a crucial role. For 2-alkynyl benzoic acids the selectivity of the reaction can be controlled by adjusting the local concentration of gold catalyst in the guanidinium functionalized  $M_{12}L_{24}$  nanosphere.

## Introduction

Transition metal catalysis is a key technology for sustainability, and as such, key for the future development of our society. Optimization of transition metal catalysts has led to more efficient reactions, facilitating the development of important chemical processes to produce fine and bulk chemicals.<sup>[1,2]</sup> Typically, the performance of a transition metal catalyst is tuned by the modification of the electronic and steric properties of the ligands that are coordinated to the metal.<sup>[3]</sup> Furthermore, in gold catalysis the counter anions can also play a pivotal role.<sup>[4]</sup> Although the classic approach has provided tremendous advance in the field, the development of new strategies to boost the range, efficiency and selectivity of transition metal-catalyzed reactions are necessary.

Supramolecular concepts<sup>[5]</sup> have evolved in the past decades as complementary strategies to control the key parameters of transition metal catalysts. Next to supramolecular ligands<sup>[6]</sup> and substrate orientation<sup>[7]</sup> by supramolecular interactions between the substrate and catalysts, control of catalyst properties via the second coordination sphere around transition metal

complexes appeared as an interesting strategy.<sup>[8]</sup> Different approaches to catalyst encapsulation have been developed in the recent years. Cages have been used to promote various organic reactions,<sup>[9]</sup> but also to encapsulate transition metal complexes affording catalysts featuring high degree of the selectivity and activity.<sup>[10]</sup>

We have introduced template-ligand approaches to catalyst encapsulation, and have used this to control a variety of reactions.<sup>[11]</sup> Recently, we extended the approach from single metal encapsulation to multiple catalyst encapsulation, by using the chemistry developed by Fujita to generate  $M_{12}L_{24}$  type spheres.<sup>[12]</sup> Also these assemblies can be easily synthesized by mixing the building block (typically bent bis-pyridyl ligands) with the appropriate amount of palladium or platinum. Functional groups can be installed at the inside of the nanosphere by introducing them at the proper position of the building block.<sup>[13]</sup> In a first approach, we functionalized building blocks with phosphine-gold complexes, and studied the effect of the high local concentration of catalysts in these nanospheres, and observed increased activity and change of selectivity in several reactions.<sup>[14]</sup>

More recently we introduced guanidinium moieties in the building blocks, generating nano-spheres with high local concentration of these hydrogen bond donor groups (Figure 1a).<sup>[15]</sup> The guanidinium spheres bind strongly sulfonate-containing guests such as TPPMSAu complexes (Figure 1b). Carboxylate-containing guests are also bound, but significantly weaker. This provides a system, coined the nano-concentrator, that can host a wanted number of catalysts, while the remaining guanidinium groups present in the sphere can pre-organize substrate molecules that contain a carboxylic group. The system was applied in the cycloisomerization of 4-pentynoic acid, providing enhanced rates and also allowing substrate selective catalysis.<sup>[15]</sup> In more recent contributions, we demonstrated that the nano-concentrator can improve reaction rates of catalytic processes that operate via bimetallic inter-

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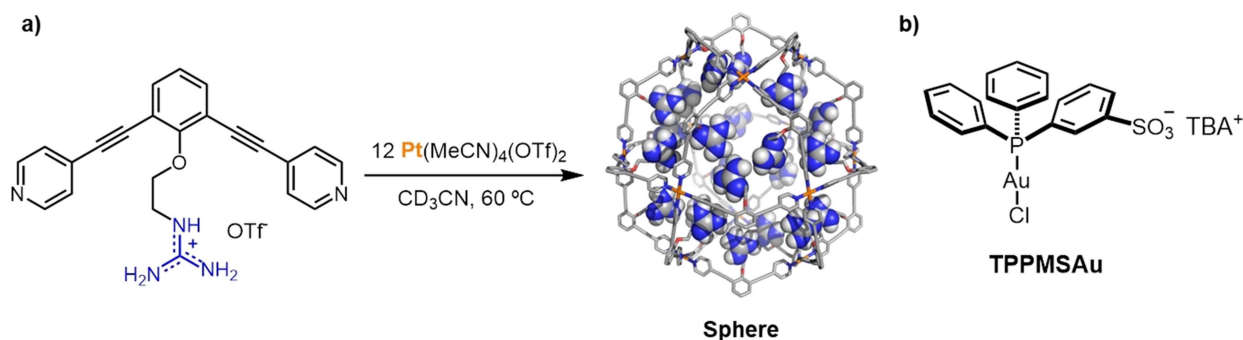


Figure 1. a) Synthesis of guanidinium functionalized nanosphere, b) Gold catalyst used in this work (TBA = tetrabutylammonium)

mediates, by generating high local concentrations of catalysts. The catalytic performance of Cu(I) complexes in cycloisomerization reactions, as well as the electrochemical water oxidation using ruthenium complexes were substantially improved.<sup>[16]</sup>

In this work we expand the application of the nano-concentrator to the gold-catalyzed cyclization of more challenging internal acetylenic acids. The nano-concentrator effect was also studied in the cyclization of 2-alkynyl benzoic acids. We have not only observed enhanced reaction rates, but also demonstrate the ability to control the selectivity of the transformation by adjusting the local concentration of catalyst within the assembly.

## Results and Discussion

We first focused our attention on the cyclization of 4-hexynoic acid (**1**).<sup>[17,18]</sup> The catalytic reactions were carried out using the same conditions as previously applied for the cycloisomerization of 4-pentynoic acid;<sup>[15]</sup> room temperature in  $\text{CD}_3\text{CN}$  as solvent. The reaction progress was monitored by  $^1\text{H}$  NMR spectroscopy. The active catalytic species ( $\text{TPPMSAu}^+$ ) were generated *in situ* by treating the Au chloride complex with  $\text{AgOTf}$ . In the cases in which the sphere and catalysts were combined, four equivalents of the gold complex with respect the sphere were used, in order to leave enough guanidinium moieties available to interact with the carboxylic groups of the

substrate. Table 1 shows the results that clearly visualize the nanosphere effect, whereas an extensive table with control experiments is provided in the supporting information (Table S1).

The gold catalyst in absence of cage and base is completely inactive for the cycloisomerization of **1** (entry 1), which is different from what we observed previously for 4-pentynoic acid,<sup>[15]</sup> highlighting the difference in reactivity of the substrates.<sup>[18]</sup> When the gold catalyst was applied in the presence of sphere or with a catalytic amount of base, the formation of product **3** was observed, although only in low yields (entries 2 and 4). When the nano-concentrator was combined with gold and a catalytic amount of triethylamine, full conversion was achieved in 8 hours (TON=20). The major product of the cyclization reaction is the 5-membered ring product (**3**), although some amount of the 6-membered ring product (**2**) was observed (entry 3). Under the applied conditions, part of compound **1** is deprotonated, which leads to binding of the substrates to the guanidinium groups within the sphere, close to the gold centers, where it undergoes cyclization.

We previously proved the ability of the nano-concentrator to encapsulate up to 24 TPPMSAu by diffusion-ordered NMR spectroscopy (DOSY) and mass spectrometry.<sup>[15]</sup> The supramolecular binding of sulfonated complexes in the nano-concentrator provides an easy manner to study the effect of local catalyst concentration on catalyst performance, as only the sphere/catalyst ratio needs to be adapted. Therefore, we decided to study this effect with the guanidinium functionalized nano-sphere (Table 2). The reactions were carried out by keeping the concentration of base and catalyst constant, and the local concentration of catalyst in the sphere was modified by changing the amount of sphere. In this way, catalytic systems were generated in which the average number of gold complexes per sphere ranged from 2 to 24, which translates to estimated local concentration from 0.09 to 1.07 M (Table 2).<sup>[14a]</sup> The local concentration of gold catalyst has a small effect on the selectivity, as product **2** formed in small amounts in all experiments (~10–15%) being the lowest with one gold per sphere (entry 1). The local concentration of gold catalyst does affect the reaction rate, as higher local concentration resulted in lower conversion.

**Table 1.** Cyclization of 4-hexynoic acid (**1**) under various conditions.<sup>[a]</sup>

Entry	Conditions	Conv. <sup>[b]</sup> [%]	<b>2</b> <sup>[b]</sup> [%]	<b>3</b> <sup>[b]</sup> [%]
1	TPPMSAu	0	–	–
2	TPPMSAu + Sphere	13	0	13
3	TPPMSAu + Sphere + $\text{Et}_3\text{N}$	100	17	83
4	TPPMSAu + $\text{Et}_3\text{N}$	31	0	31

[a] Reaction conditions: [**1**] = 10 mM, [TPPMSAu] = 0.5 mM (activated *in situ* by adding an equal equivalent of  $\text{AgOTf}$ ), [ $\text{Et}_3\text{N}$ ] = 0.5 mM, [Sphere] = 0.125 mM,  $\text{CD}_3\text{CN}$ , RT, 8 h. [b] Conversion and selectivity determined by  $^1\text{H}$  NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

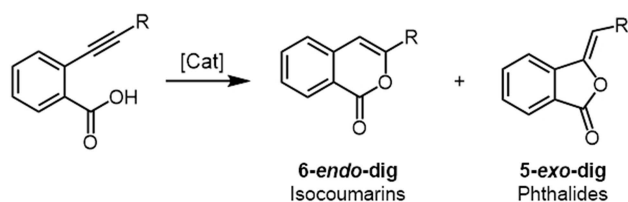
Once proven that our catalytic system can promote the cycloisomerization of internal alkynes, we decided to study its effect on the cyclization 2-alkynyl benzoic acids. This type of substrates is especially interesting because depending on the catalytic system applied,<sup>[19]</sup> the reaction can proceed to yield the 6-*endo*-dig product, also known as isocoumarins, or the 5-*exo*-dig compound (phthalides) (Scheme 1), which are known to be biologically active molecules.<sup>[20]</sup>

We decided to study the effect of local catalyst concentration on the cyclization of compound **4** (Scheme 2). This substrate contains two carboxylic groups which can potentially attack the triple bond, and as a result a variety of products can be formed. One of these moieties is directly pointing to the alkyne, while the other one is connected to a flexible linker.

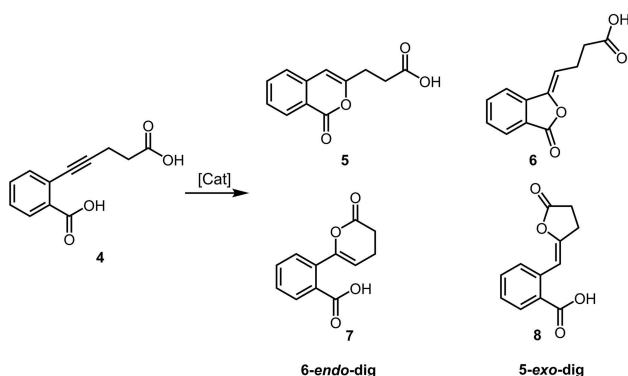
**Table 2.** Cyclization of 4-hexynoic acid (**1**) at different local concentration of Au in the nanosphere.<sup>[a]</sup>

Entry	TPPMSAu/Sphere	Local [Au] <sup>[b]</sup> [M]	Conv. <sup>[c]</sup> [%]	2/3 <sup>[c]</sup>
1 <sup>[d]</sup>	2	0.09	100	0.1
2 <sup>[e]</sup>	4	0.18	100	0.2
3 <sup>[f]</sup>	12	0.54	82	0.2
4 <sup>[g]</sup>	18	0.80	71	0.2
5 <sup>[h]</sup>	24	1.07	54	0.2

[a] Reaction conditions: [1] = 10 mM, [TPPMSAu] = 0.5 mM (activated *in situ* by adding an equal equivalent of AgOTf), [Et<sub>3</sub>N] = 0.5 mM, CD<sub>3</sub>CN, RT, 8 h. [b] Local concentration of gold complex within the sphere.<sup>[14a]</sup> [c] Conversion and selectivity determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [d] [Sphere] = 0.25 mM [e] [Sphere] = 0.125 mM. [f] [Sphere] = 0.042 mM, [g] [Sphere] = 0.028 mM, [h] [Sphere] = 0.021 mM.



**Scheme 1.** Cycloisomerization of internal alkynes to yield either the 6-*endo*-dig product (isocoumarins) or the 5-*exo*-dig compound (phthalides).



**Scheme 2.** Cyclization of **4** and potential products that can form

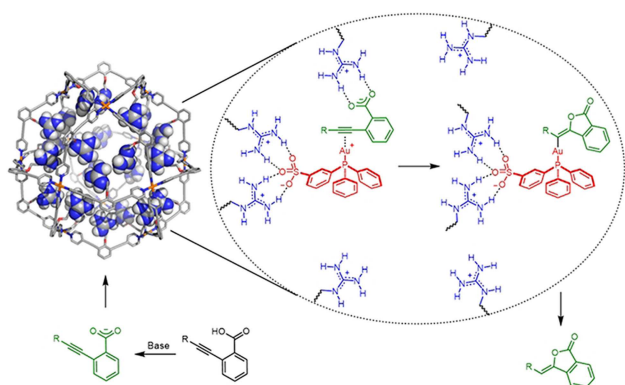
Table 3 shows the catalytic results for the cycloisomerization of **4** (for control experiments see Table S2 in the supporting information). From all the possible products, only the corresponding phthalide and isocoumarin (**5** and **6**, respectively) were observed in all the experiments. This is in contrast with related diol additions to internal alkynes, in which a two-fold addition to form spiroketals was observed.<sup>[21]</sup> The reaction with the cationic gold complex is very fast, providing almost selectively the isocoumarin **5** with 100% conversion in one hour (entry 1). Clearly, the nucleophilic attack from the carboxylate at the aromatic ring is much faster than that of the competing aliphatic carboxylate.

The addition of guanidium sphere to the reaction media slows down the rate of the reaction as 100% conversion is reached after 6 hours instead of 1 hour, and it also changes the selectivity of the process. Formation of phthalide **6** is increased under these conditions (entry 2). We attribute this result to an homoconjugation process<sup>[22]</sup> that is taking place between the two carboxylic groups of the substrate. Homoconjugation can favor the stabilization of ionic intermediates by hydrogen bonding, and it is well-known to be important in acetonitrile due to its low ion solvating ability.<sup>[23]</sup> This process provides a small amount of deprotonated substrate that is able to interact with the guanidinium groups of the sphere. Interestingly, when a catalytic amount of base was used in combination with the encapsulated gold catalyst, effectively organizing the substrate close to the bound catalyst in the sphere via interaction with the guanidinium groups, the selectivity of the reaction switched, affording compound **6** as the major product (entry 3). The rate of the reaction is slower than without a catalytic amount of base, suggesting that the generation of isocoumarin is inhibited while the production of the phthalide is accelerated (*vide infra*). The difference between the experiment in absence and presence of base (Entry 2 and 3) is just the amount of substrate that is deprotonated and pre-organized with respect to the catalyst. The interaction of the deprotonated **4** with the guanidinium groups of the sphere proceeds via the aromatic carboxylic moiety, as aromatic carboxylic acids are more acidic than the alkylic congeners, therefore being easier to deprotonate by a mild base as Et<sub>3</sub>N (Scheme 3).<sup>[24]</sup> This, in turn, most

**Table 3.** Cyclization of 2-alkynyl benzoic acid **4**.<sup>[a]</sup>

Entry	Conditions	t <sup>[h]</sup>	Conv. <sup>[b]</sup> [%]	5/6 <sup>[b]</sup>
1	TPPMSAu	1	100	13.0
2	TPPMSAu + Sphere	6	100	2.7
3	TPPMSAu + Sphere + Et <sub>3</sub> N	10	100	0.4
4	TPPMSAu + Et <sub>3</sub> N	10	28	3.4

[a] Reaction conditions: [4] = 10 mM, [TPPMSAu] = 0.5 mM (activated *in situ* by adding an equal equivalent of AgOTf), [Et<sub>3</sub>N] = 0.5 mM, [Sphere] = 0.125 mM, CD<sub>3</sub>CN, RT. [b] Conversion and selectivity determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.



**Scheme 3.** Schematic representation of the catalytic system in the presence of base

likely preorganizes the substrate to favor formation of the 5-membered ring.

Finally, the control reaction where the gold catalyst and a catalytic amount of triethylamine are present (in absence of sphere) provided low conversions even after 10 h reaction time, forming 5 as the dominant product.

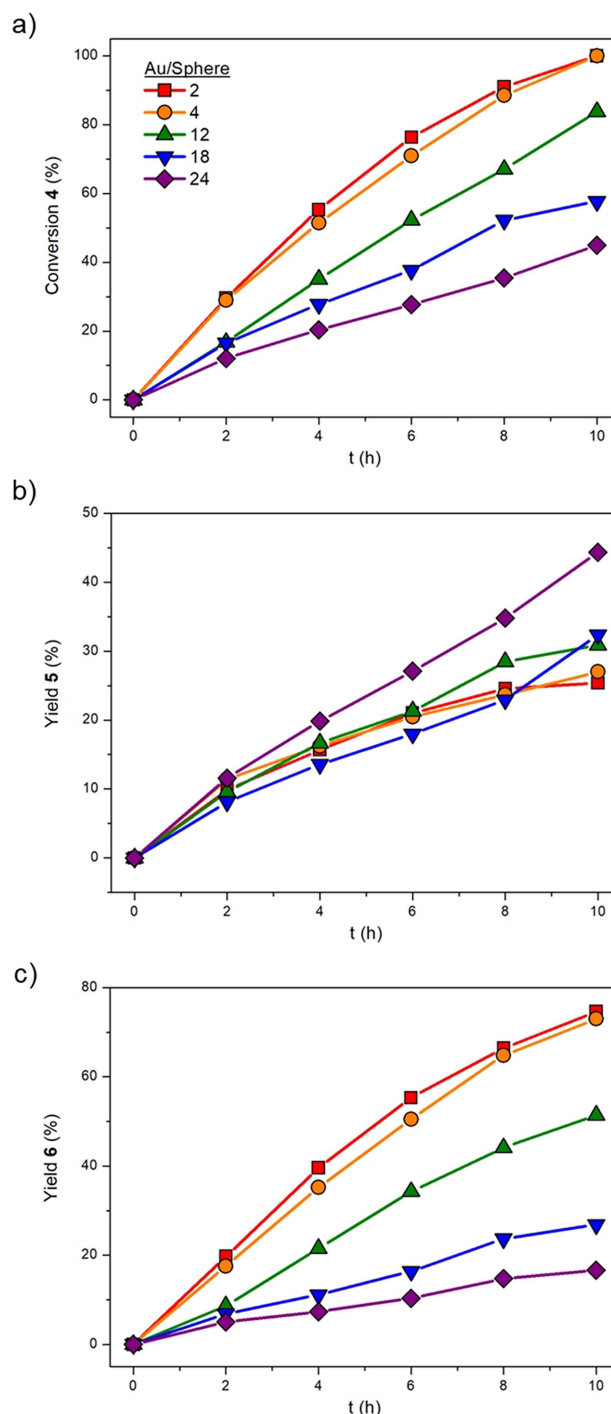
Next, we explored the effect of the local concentration of catalysts in the sphere. Table 4 shows the results obtained when the reaction was performed at constant gold catalyst concentration, but at different  $\text{Au}^+$ /Sphere ratio by adjusting the sphere concentration. The regioselectivity of the reaction is strongly influenced by the local gold concentration. When an average of two gold catalysts per sphere was used, the maximum amount of product 6 was achieved (Table 4, entry 1). If the number of gold catalysts per sphere is increased, the regioselectivity of the reaction is changed in favor of compound 5 (compare entries 1–5 in table 4).

To further understand the local concentration effect in this transformation we monitored the reaction in time and analyzed product formation (5 and 6) under various conditions (at different Au/sphere ratios, Figure 2). Figure 2b shows that the rate in the formation of product 5 does not vary significantly as function of the local gold catalyst concentration. This is different for the formation of 6 which, as can be seen in Figure 2c, is

**Table 4.** Cyclization of 2-alkynyl benzoic acid 4 at different local concentration of Au in the nanosphere.<sup>[a]</sup>

Entry	TPPMSAu/Sphere	Local [Au] <sup>[b]</sup> [M]	Conv. <sup>[c]</sup> [%]	5/6 <sup>[c]</sup>
1 <sup>[d]</sup>	2	0.09	100	0.3
2 <sup>[e]</sup>	4	0.18	100	0.4
3 <sup>[f]</sup>	12	0.54	82	0.7
4 <sup>[g]</sup>	18	0.80	71	1.2
5 <sup>[h]</sup>	24	1.07	54	1.7

[a] Reaction conditions: [4] = 10 mM, [TPPMSAu] = 0.5 mM (activated *in situ* by adding an equal equivalent of AgOTf), [Et<sub>3</sub>N] = 0.5 mM, CD<sub>3</sub>CN, RT, 10 h. [b] Nano-local concentration of gold complex within the sphere.<sup>[14a]</sup> [c] Conversion and selectivity determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [d] [Sphere] = 0.25 mM [e] [Sphere] = 0.125 mM. [f] [Sphere] = 0.042 mM, [g] [Sphere] = 0.028 mM, [h] [Sphere] = 0.021 mM.



**Figure 2.** Reaction progress for the conversion of 4 (a), formation of 5 (b) and formation of 6 (c) at different TPPMSAu/Sphere ratios. For reaction conditions see Table 4.

strongly dependent on the local concentration of gold. This effect can be ascribed to either the high local catalyst concentration, or the available guanidinium groups that are accessible to pre-organize the substrate within the sphere. If the gold concentration in the sphere is increased, the number of available guanidinium groups for substrate binding is

decreased as they are involved in binding to the sulfonate groups.

To further evaluate the role of the guanidinium groups of the assembly in the selectivity of the transformation, the reaction was carried out in the presence of *p*-toluene-sulfonate (TolSO<sub>3</sub>) as a competitive guest.<sup>[15]</sup> In such experiment, the local concentration of gold remains the same, but with increasing amount of TolSO<sub>3</sub> the number of guanidinium groups available for substrate binding decreases. Indeed, in the presence of increasing amounts of TolSO<sub>3</sub>, the rate of the reaction decreases and the selectivity of the reaction changes in favor of the formation of **5** (Table 5). These catalytic results follow the same trend as those reported in Table 4. Therefore, the high selectivity for product **6** at low local concentration of gold can be ascribed to the interaction of the guanidinium groups of the sphere with the substrate during the reaction, which under these conditions are available. These results show that our catalytic system controls the selectivity by enhancing the rate of the formation of product **6** when guanidinium binding sites are available, while product **5** is formed in rates that do not depend on local gold concentration or availability of guanidinium sites.

As the carboxylic moiety bonded to the flexible part of compound **4** is not reacting with the triple bond, we wondered

**Table 5.** Effect of the competitive guest on the cyclization of **4**.<sup>[a]</sup>

Entry	Conditions	Conv. <sup>[b]</sup> [%]	5/6 <sup>[b]</sup>
1 <sup>[c]</sup>	TPPMSAu + Sphere + Et <sub>3</sub> N + TolSO <sub>3</sub> (5 eq)	77	0.4
2 <sup>[d]</sup>	TPPMSAu + Sphere + Et <sub>3</sub> N + TolSO <sub>3</sub> (10 eq)	77	0.6
3 <sup>[e]</sup>	TPPMSAu + Sphere + Et <sub>3</sub> N + TolSO <sub>3</sub> (15 eq)	61	1
4 <sup>[f]</sup>	TPPMSAu + Sphere + Et <sub>3</sub> N + TolSO <sub>3</sub> (20 eq)	41	1.5

[a] Reaction conditions: [**4**] = 10 mM, [TPPMSAu] = 0.5 mM (activated *in situ* by adding an equal equivalent of AgOTf), [Et<sub>3</sub>N] = 0.5 mM, [Sphere] = 0.125 mM, CD<sub>3</sub>CN, RT, 10 h. [b] Conversion and selectivity determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c] [TolSO<sub>3</sub>] = 0.625 mM, [d] [TolSO<sub>3</sub>] = 1.25 mM. [e] [TolSO<sub>3</sub>] = 1.88 mM, [f] [TolSO<sub>3</sub>] = 2.5 mM.

**Table 6.** Cyclization of 2-alkynyl benzoic acids **9** and **12**.<sup>[a]</sup>

Entry	Conditions	R	t <sup>[h]</sup>	Conv. <sup>[b]</sup> [%]	Iso/Pth <sup>[b]</sup>
1	TPPMSAu	OH	1	100	Iso
2	TPPMSAu	CH <sub>3</sub>	1	100	Iso
3	TPPMSAu + Sphere	OH	8	100	2.5
4	TPPMSAu + Sphere	CH <sub>3</sub>	8	100	3.9
5	TPPMSAu + Sphere + Et <sub>3</sub> N	OH	24	100	0.8
6	TPPMSAu + Sphere + Et <sub>3</sub> N	CH <sub>3</sub>	24	100	0.9
7	TPPMSAu + Et <sub>3</sub> N	OH	24	20	2.6
8	TPPMSAu + Et <sub>3</sub> N	CH <sub>3</sub>	24	16	2.0

[a] Reaction conditions: [Substrate] = 10 mM, [TPPMSAu] = 0.5 mM (activated *in situ* by adding an equal equivalent of AgOTf), [Et<sub>3</sub>N] = 0.5 mM, [Sphere] = 0.125 mM, CD<sub>3</sub>CN, RT. [b] Conversion and selectivity determined by <sup>1</sup>H NMR spectroscopy using trimethoxybenzene as internal standard.

what its role in the reaction process was. For this purpose, the cyclization of analogous compounds to **4**, containing an alcohol (**9**) and an alkyl chain (**12**) instead of carboxylic acid were studied (Table 6).

Similar trends as for substrate **4** were found. The reaction is again very fast by using the single gold catalyst, but in this case the corresponding isocoumarins were obtained selectively (entries 1 and 2). By using the gold catalyst encapsulated in the guanidinium sphere the reaction takes 8 hours to reach full conversion for both substrates, and the selectivity towards the isocoumarin product decreased (entries 3 and 4). When a catalytic amount of triethylamine was combined with gold and sphere, the corresponding phthalide was observed to be the major product (entries 5 and 6), although in this case the 5-membered ring product is generated in lower amount than was found for substrate **4** (Table 3 entry 3). Interestingly, 24 h were necessary to reach full conversion, which is much longer than we observed for compound **4** under the same conditions. This suggests that the presence of the second carboxylic group in compound **4** is able to accelerate the rate of the reaction. Low conversions for both substrates were observed in experiments with gold complex as catalyst in presence of a catalytic amount of base and absence of sphere (entry 7 and 8).

The effect of local concentration of gold catalyst was also investigated for substrates **9** and **12**. Table 7 shows the conversion and the selectivity of the reaction at 24 hours. Increasing the amount of gold catalysts within the nanosphere lowers in general the conversion, in line what we observed for **4**.

In terms of selectivity, both substrates follow the same trend as observed for **4**. At low local concentration of gold, the amount of corresponding phthalide generated is higher. Interestingly, the group attached to the alkylic chain of the substrates seems to influence the products distribution when the highest amount of guanidinium groups within the nano-concentrator are available (compare entries 1 and 5 in Table 7 with entry 1 in Table 4). Under those conditions the substrate that provides that highest amount of phthalide is **4**. This could be due to the different acidity of the groups of the flexible linker of the substrates, although further experiments are necessary to understand this trend in detail.

**Table 7.** Cyclization of 2-alkynyl benzoic acids **9** and **12** at different local concentration of Au in the nanosphere.<sup>[a]</sup>

Entry	TPPMSAu/Sphere	R	Conv. <sup>[b]</sup> [%]	Iso/Pth <sup>[b]</sup>
1 <sup>[c]</sup>	2	OH	100	0.6
2 <sup>[d]</sup>	4	OH	100	0.8
3 <sup>[e]</sup>	12	OH	61	1.5
4 <sup>[f]</sup>	24	OH	45	2.2
5 <sup>[c]</sup>	2	CH <sub>3</sub>	100	0.8
6 <sup>[d]</sup>	4	CH <sub>3</sub>	100	0.9
7 <sup>[e]</sup>	12	CH <sub>3</sub>	71	1.9
8 <sup>[f]</sup>	24	CH <sub>3</sub>	44	5.2

[a] Reaction conditions: [Substrate] = 10 mM, [TPPMSAu] = 0.5 mM (activated *in situ* by adding an equal equivalent of AgOTf), [Et<sub>3</sub>N] = 0.5 mM, CD<sub>3</sub>CN, RT, 24 h. [b] Conversion and selectivity determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c] [Sphere] = 0.25 mM, [d] [Sphere] = 0.125 mM, [e] [Sphere] = 0.042 mM, [f] [Sphere] = 0.021 mM.

## Conclusions

In conclusion, we have applied our previously reported nano-concentrator in combination with TPPMSAu complexes in the cycloisomerization of various substrates. For the challenging internal alkyne, 4-hexynoic acid (1), we observed that pre-organization of the catalyst and the substrate in the nanosphere dramatically increases the conversion. At higher local concentration of gold catalyst, with less guanidinium sites available for binding the substrate, the reaction conversion dropped. Although the 5-membered ring lactone was the dominant product, some 6-membered ring product was also formed. In the cyclization of 2-alkynyl benzoic acids the selectivity of the transformation is very dependent on the amount of available binding sites of the sphere. We found that for this reaction the pre-organization of the substrate plays a crucial role; at high catalyst loading via supramolecular binding to the guanidinium groups, less binding sites are available for binding to the substrate. With these results we show that by changing the local concentration of catalyst in the nanosphere we not only can change the reaction rate, as previously reported, but also can control the selectivity of the reaction. Current work in our laboratory is focusing in expanding this concept to other transition metal-catalyzed reactions involving more sophisticated mechanisms, and also in the development of tandem catalytic processes within the sphere.

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** gold catalysis · supramolecular chemistry · nano-concentrator · pre-organization · selectivity

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