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Substrate selectivity in the alkyne hydration mediated by NHC–Au(I) controlled by encapsulation of the catalyst within a hydrogen bonded hexameric host†

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Significant alterations in the substrate selectivity in the alkyne hydration reaction catalyzed by NHC–Au(I) **1 are observed as a consequence of encapsulation of the homogeneous catalyst within a hexameric resorcin[4]arene based hydrogen bonded self-assembled host.**

Selectivity is a key aspect in catalysis, in particular it is referred to as the preferential formation of one out of several possible products. Systems developed to display substrate selectivity using a mixture of substrates all together delivered to the catalyst are rare. Heterogeneous catalysts are intrinsically more easily tunable to provide substrate selectivity because of their porosity properties¹ and examples of substrate selectivity are known also with catalytic polymers^{2,3} and imprinted polymers.⁴ Substrate selectivity for homogeneous catalysts is limited mainly to kinetic resolution of racemates in which one of the enantiomers reacts more rapidly than the other.⁵ Some other examples of substrate selectivity are described in which substrate mixtures with large differences in the structure of the reagents are used. Recent examples include substrate selectivity that distinguishes between aromatic and aliphatic alkenes or alcohols.^{6–8} A more general strategy involves substrates sharing the same functional group but bearing extra functionalities. Most frequent examples are based on hydrogen bonding moieties^{9–13} or other weak intermolecular interactions that ensure preorganization with the catalyst thus favouring one substrate over the other. In other words the “homologous” substrates tested differ significantly in another part of the molecule.

Catalytic systems in which substrates differ only to a small extent in positions remote from the reactive center, lacking extra interaction with the catalyst, are indeed rare. In such cases substrate selection is usually based on steric interactions^{14–16} often using well defined supramolecular capsules imparting rigid steric constraints, thus resembling shape selectivity with zeolites and aided also by the hydrophobic effect when working in water as solvent.^{17,18} This approach however requires that each time individual capsules should be designed and synthesized to meet the requirements of the given reaction.

Enzymes are outstanding examples of product selective catalysts but they are also impressive examples of substrate selectivity^{19–22} (Fig. 1), thereby being an excellent source of inspiration. To implement such a concept in homogeneous catalysis a possible approach is developed, which involves surrounding the homogeneous catalyst with a capsular host. In this case the substrates are forced to be accommodated in the residual cavity left by the catalyst thus experiencing supramolecular interactions with the inner surfaces of the

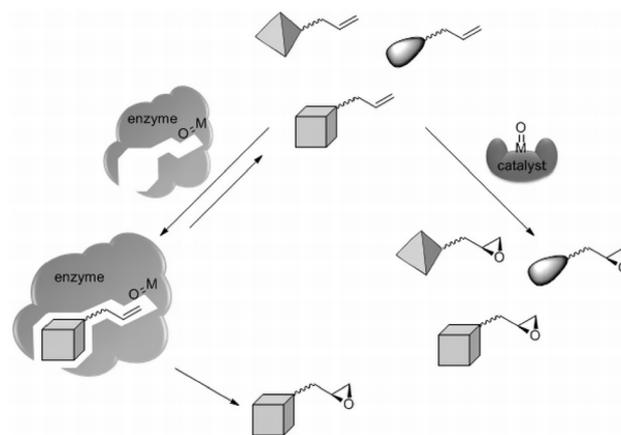


Fig. 1 Example of substrate selectivity displayed by enzymes involved in the initial formation of the substrate–enzyme adduct. Conversely, a common organometallic catalyst is much less substrate selective because of poor interactions with the substrates.

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capsule as well as with the catalyst itself. Overall, a higher level of steric and electronic restrictions is provided thus favoring selection of the substrates, a property that does not apply to free catalysts in solution in competitive experiments.

Gold is known to promote alkyne hydration,²³ and recently we disclosed the effect of encapsulation of a (i-Pr-NHC)Au(OTf) complex **1** ([trifluoromethanesulfonyl[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I)]) within a self-assembled hexameric hydrogen bonded resorcin[4]arene capsule $2_6 \cdot 8H_2O$,²⁴ observing that encapsulation unexpectedly influenced the product selectivity in the alkyne hydration reaction.²⁵ Steric requirements imparted by the host in the residual space available for the substrate within the cavity of the hexamer are responsible for the product selectivity observed. We anticipated that an analogous principle could lead to interesting substrate selectivity properties based mainly on steric and geometric matching of the substrate in the residual cavity left by the encapsulated **1**. It is worth noting that for the hexameric capsule the substrate access to the encapsulated catalyst requires breaking of several H-bonds and almost complete disassembly of one resorcin[4]arene unit. Because of this it is expected that the differences observed in substrate selectivity would not be extremely high because the substrate is not selected for its capacity to pass through the openings but rather to match with the available cavity within the capsule. Moreover, the versatility provided by a large capsule in terms of possible hosts is expected to be compensated by a lower selectivity. Recently other Au(I) catalysts have been demonstrated to be suitable guests for the hexameric capsule pointing the attention to the effect of the encapsulation procedure on the final species hosted and their affinity for the cavity.²⁶

Herein we report on the effect of encapsulation of the Au(I) catalyst **1** within the capsule $2_6 \cdot 8H_2O$ on substrate selectivity in the hydration of terminal alkynes for a series of substrates, differing structurally only in a remote portion with respect to the reactive triple bond (Fig. 2). These were fed to the catalytic system all together in competitive experiments.

Initially we investigated the substrate selectivity displayed by **1** towards aliphatic alkynes. In particular we selected two flexible alkynes and a cyclic analogue. Ethynylcyclohexane **6**, isomeric 1-octyne **7** and 1-dodecyne **8** were investigated at 40 °C with 5% mol of catalyst with respect to each substrate (Fig. 3). The reaction showed a short induction period for all substrates, indicative of the initial slow formation of the truly active catalytic species probably due to equilibria involving different anionic species as counterions.²⁷ The free complex converted quantitatively all three substrates within 250 minutes. The kinetic profiles show that shorter time (95 minutes) is required to reach 50% conversion to the corresponding hydrated carbonyl compound in the case of **6**, while longer times are required in the case of **7** and **8** (Fig. 3).

The reaction became slower when **1** was encapsulated within $2_6 \cdot 8H_2O$ observing that the maximum yield in ketone achieved after 4 hours was lower than 50% (Fig. 4). Under these conditions the induction time is no longer present. The reactions with the encapsulated catalyst **1** are sluggish

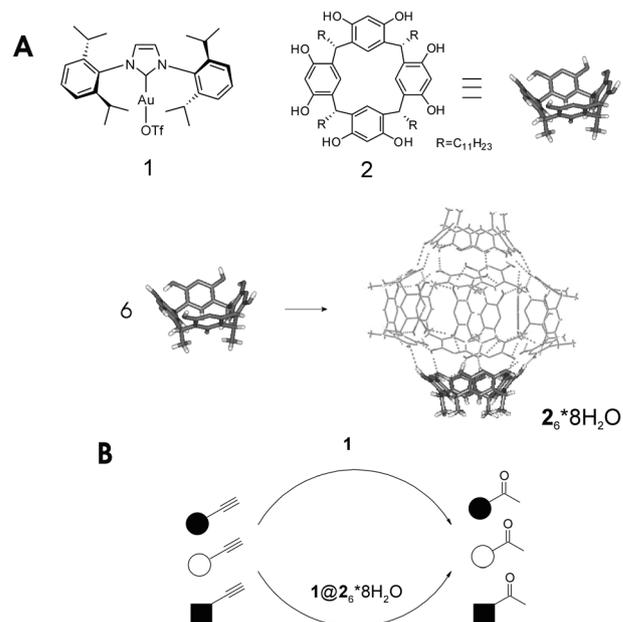


Fig. 2 (A) Chemical structure of (i-Pr-NHC)Au(OTf) complex **1** and of resorcin[4]arene **2** that in wet organic solvent self-assembles forming the hexamer $2_6 \cdot 8H_2O$. (B) Comparison of the substrate selectivity displayed by free and encapsulated catalyst **1** in the hydration reaction of alkynes.

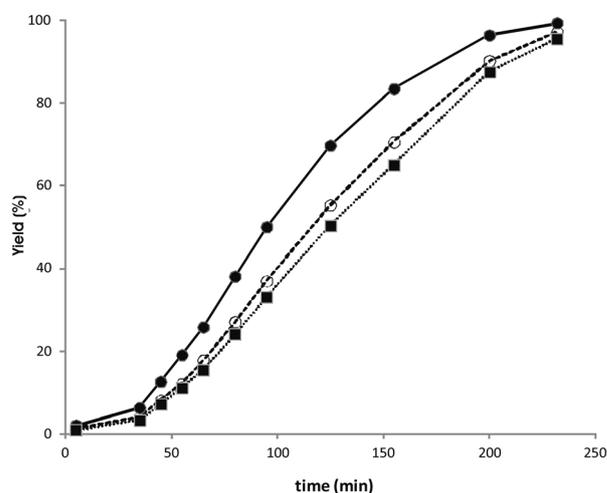


Fig. 3 Competitive substrate selective hydration of ethynylcyclohexane **6** (●), 1-octyne **7** (○), 1-dodecyne **8** (■) catalyzed by **1** free in water saturated benzene-*d*₆ at 40 °C. [6] = [7] = [8] = 65 mM, [1] = 3.3 mM.

compared to those with other known systems,²⁸ but this is an expected result since the substrate has to sneak into the cavity through the seam of hydrogen bonds of $2_6 \cdot 8H_2O$ and this decreases significantly the rate of the reaction.²⁵ Notably, the reaction profiles show a significant preference for the encapsulated Au(I) catalyst for the cyclic alkyne **6**. After 155 minutes substrate **6** was converted by about 48%, while **7** and **8** were converted only by 25% and 21%, respectively. This preference was quantified by the initial reaction rate determined from the slope in the kinetic profile for each substrate. The values observed for the encapsulated **1** were compared to those

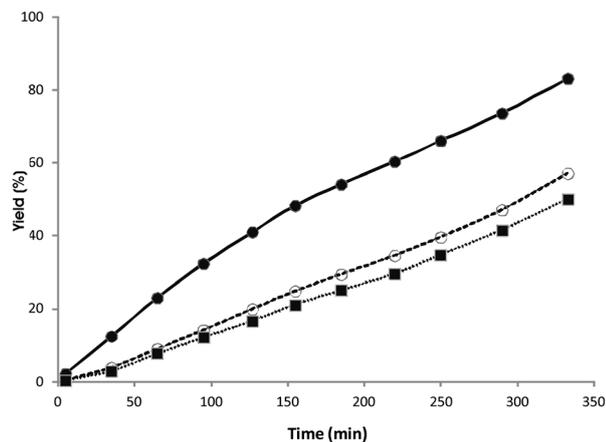


Fig. 4 Competitive substrate selective hydration of ethynylcyclohexane **6** (●), 1-octyne **7** (○), 1-dodecyne **8** (■) catalyzed by **1**@**2**₆·8H₂O in water saturated benzene-d₆ at 40 °C. [6] = [7] = [8] = 65 mM, [1] = 3.3 mM, [2] = 33 mM.

obtained for free **1** analyzing the maximum rate after the induction time. In the case of the cyclic alkyne **6**, the initial rate with the supramolecular catalyst is about three times higher than that obtained for the other two substrates **7** and **8** (**6**:**7**:**8** = 3.4:1.3:1.0, Fig. 4), while the free complex provides almost the same slope for all the alkynes (**6**:**7**:**8** = 1.5:1.0:1.0, Fig. 3).

A possible explanation for this phenomenon lies in the markedly different shape of the cyclic substrate compared to the linear ones. Probably **6** fits better in the space left by the gold complex within the hexamer cavity **2**₆·8H₂O. Conversely, linear substrates **7** and **8**, which in their extended conformation are approximately 1.4 and 2.1 times longer than **6** respectively, need to partially fold in order to fit into the cavity left by catalyst **1** and this decreases their reactivity.

Subsequently, three rigid aromatic alkynes unable to adopt different conformations were evaluated in competitive experiments. Phenylacetylene **9**, *p*-methyl-phenylacetylene **10** and *p*-(*t*-butyl)-phenylacetylene **11** characterized by the same general shape but different length and steric hindrance were reacted at 80 °C instead of at 40 °C because of the intrinsic lower activity of aromatic vs. aliphatic alkynes. Free catalyst **1** in water saturated benzene-d₆ appeared to slightly prefer substrates **10** and **11** with respect to **9** (Fig. 5). This is expected because the *p*-substituted phenylacetylenes with aliphatic residues are characterized by higher electron density on the triple bond and this enhances their coordination to Au(I) and their reactivity. After 92 minutes the substrates **9**, **10** and **11** provided the corresponding hydration products in 37, 52 and 55% yield, respectively. Determination of the initial rate of reaction for the three aromatic substrates showed that the more electron rich **11** reacted one and a half times faster than the less electron rich **9** (**9**:**10**:**11** = 1.0:1.4:1.5).

Apart from an expected decrease in activity with respect to the free catalyst, a completely reversed substrate selectivity was observed when catalyst **1** was encapsulated within **2**₆·8H₂O. The smaller aromatic alkyne of the series **9** reacted much faster than those of the other two aromatic substrates **10** and **11** (Fig. 6).

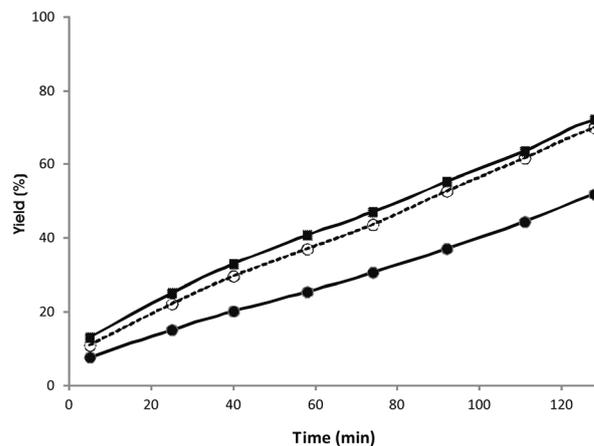


Fig. 5 Competitive substrate selective hydration of phenylacetylene **9** (●), *p*-methyl-phenylacetylene **10** (○) and *p*-(*t*-butyl)-phenylacetylene **11** (■) catalyzed by free **1** in water saturated benzene-d₆ at 80 °C. [9] = [10] = [11] = 65 mM, [1] = 3.3 mM.

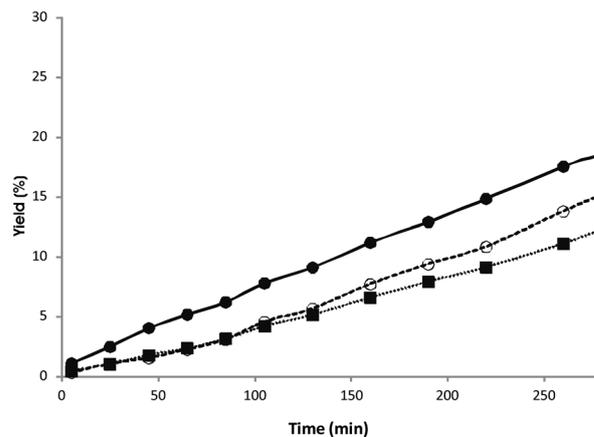


Fig. 6 Competitive substrate selective hydration of phenylacetylene **9** (●), *p*-methyl-phenylacetylene **10** (○) and *p*-(*t*-butyl)-phenylacetylene **11** (■) catalyzed by **1**@**2**₆·8H₂O in water saturated benzene-d₆ at 80 °C. [9] = [10] = [11] = 65 mM, [1] = 3.3 mM, [2] = 33 mM.

After 260 minutes the amount of acetophenone produced from the hydration reaction of **9** was 18%, while **10** and **11** provided the corresponding *p*-substituted acetophenones with 14% and 11% yield, respectively. Considering the initial rate of the reactions it is evident that upon encapsulation, catalyst **1** is forced to prefer the smaller and intrinsically less reactive rigid aromatic substrate **9** by 1.6 times than the longer **11** (**9**:**10**:**11** = 1.6:1.3:1.0). The hexameric capsule **2**₆·8H₂O provides extra steric constraint for the substrate to react with catalyst **1** and this turned out to be in favor of the smaller substrate, even though it is intrinsically less reactive. Even substrate **10** appeared to be slightly more active than **11** as a further confirmation that the encapsulated Au(I) catalysts now prefers the smaller rigid aromatic substrate because this is better hosted by the cavity. It is worth noting that the differences in length among the three aromatic substrates are moderate (**9** 7.4 Å, **10** 8.1 Å and **11** 9.5 Å), but this seems

to be enough to reverse the substrate selectivity. The hydrogen bond seam that surrounds catalyst **1** provides a barrier that decreases the rate of the reaction and alters the selection rules of **1**. The relative diffusion rates for the substrates **9–11** reflect their ability to sneak into the self-assembled capsule and to match the size and shape of the residual available space present in the cavity.²⁹

In conclusion, we have demonstrated that by simply changing the second coordination sphere around a given homogeneous organometallic catalyst like **1** it is possible to enhance the substrate selectivity displayed by the catalyst towards a homologous series of substrates and, in certain cases, even reverse the order of activity of the substrates. In particular, free catalyst **1** in solution appeared to prefer aliphatic cyclic alkynes in the hydration reaction, and this effect was enhanced upon encapsulation thanks to the more compact shape of the cyclic substrate that does not have to fold up to be encapsulated. With rigid aromatic alkynes, catalyst **1** in solution preferred the more electron rich and longer substrate of the series while, after encapsulation, the substrate selectivity was reversed since the smaller substrate was better hosted within the cavity of the capsule. The differences observed are not very high, probably because of the large internal volume of the cavity that requires the presence of other solvent molecules along with catalyst **1** and substrate to ensure good stability to the assembly. Even if more eloquent examples of substrate selectivity are known with much smaller supramolecular assemblies,^{17,18} the present system represents a rather general approach that could be applied to other cationic metal catalyzed reactions. Although this interplay between the catalyst and the capsule appears to be a simplified model to mimic enzyme behavior and therefore much weaker in terms of substrate selectivity and very upstream from possible practical applications, it does prove a principle and suggest a suitable strategy to steer both substrate and product²⁵ selectivity at the same time.

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