Control of selectivity in heterogeneous catalysis by tuning nanoparticle properties and reactor residence time

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A combination of the advantages of homogeneous and heterogeneous catalysis could enable the development of sustainable catalysts with novel reactivity and selectivity. Although heterogeneous catalysts are often recycled more easily than their homogeneous counterparts, they can be difficult to apply in traditional organic reactions and modification of their properties towards a desired reactivity is, at best, complex. In contrast, tuning the properties of homogeneous catalysts by, for example, modifying the ligands that coordinate a metal centre is better understood. Here, using olefin cyclopropanation reactions catalysed by dendrimer-encapsulated Au nanoclusters as examples, we demonstrate that changing the dendrimer properties allows the catalytic reactivity to be tuned in a similar fashion to ligand modification in a homogeneous catalyst. Furthermore, we show that these heterogeneous catalysts employed in a fixed-bed flow reactor allow fine control over the residence time of the reactants and thus enables the control over product distribution in a way that is not easily available for homogeneous catalysts.

Highly selective catalysts, especially those that can be recycled readily, are vital for the development of sustainable chemical processes[1,2]. Therefore, catalytic systems in which several parameters can be tuned to achieve good product selectivity are highly desirable. For example, in homogeneous catalysis, commonly the steric and electronic features of the ancillary ligands are varied to attain a high stereoselectivity. Heterogeneous catalysts, however, have the advantages of being readily recyclable and easily adopted in a fixed-bed flow reactor. The development of novel catalytic systems that combine the advantages of homogeneous and heterogeneous catalysis is therefore a major aim of modern chemistry[1–21]. However, catalysts that allow for selectivity control of both modes are exceedingly rare.
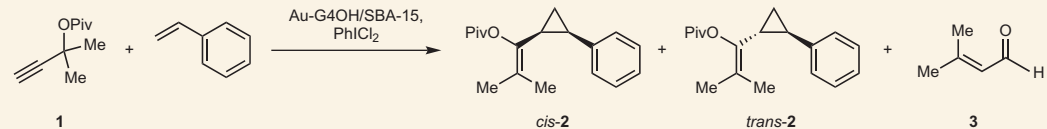
The conventional method of heterogenizing homogeneous catalysts is to graft transition-metal complex catalysts on mesoporous solid supports that have a high surface area[3,4]. It is known that surface metal sites can catalyse a variety of reactions, such as olefin metathesis[5] and Ziegler–Natta depolymerization[6]. More recently, a different approach emerged as a powerful alternative, in which metal nanoparticles are employed as catalysts for reactions that were previously catalysed soley by homogeneous catalysts[7–21]. A variety of metal nanoparticles, such as Au (refs 11–15), Ag (ref. 16), Co (ref. 17), Pd (refs 18,19) and Pt (refs 20,21) were employed to catalyse the formation of complex organic molecules with high yields and recyclability. However, only in a few cases did the metallic nanoparticles show better or different selectivity when compared to their homogeneous analogues[15].

We reported recently that polyamidoamine (PAMAM) dendrimer-encapsulated Pd and Pt clusters on mesoporous SiO$_2$ supports, when oxidized by PhICl$_2$, were active for a range of π-bond activation reactions previously catalysed only through homogeneous catalysts[19–21]. These highly active heterogeneous catalysts were generated by the reversible oxidation of metal clusters to ions, which were stabilized by both the encapsulating dendrimer and the mesoporous silica support. The formation of the

catalytically active metal ions by the addition of PhICl$_2$ and the reversibility of the cluster oxidation–reduction cycles were measured *in-situ* by X-ray absorption spectroscopy (XAS). The leaching-resistant properties of the dendrimer-encapsulated catalyst were attributed to the hydrophobic–hydrophilic repulsions between the solvent and the solid catalyst[21]. Our interest in Au catalysis[22] prompted us to consider whether this strategy would be amenable to achieving a high selectivity in Au-catalysed transformations for the preparation of complex organic molecules. In this article, we report that by replacing homogeneous AuCl$_3$ with a dendrimer-encapsulated Au nanoparticle heterogeneous catalyst, the diastereoselectivity of Au-catalysed cyclopropanation reactions can be enhanced significantly. Moreover, we demonstrate that when this heterogeneous catalyst is employed in a fixed-bed flow reactor, the catalytic reactivity and product selectivity of secondary reactions can be controlled by tuning the residence time of the reactants.

Results and discussion

Catalytic cyclopropane formation. Au clusters (2.0 ± 0.3 nm, Supplementary Fig. S1) were encapsulated in a fourth-generation (G4) PAMAM dendrimer[23,24] and loaded on SBA-15 (Au-G4OH/SBA-15), a mesoporous SiO$_2$ support with a surface area of 760 m^2 g^{-1} (ref. 25). The mesoporous silica support used in these experiments had a pore diameter of 7 ± 1 nm and therefore the dendrimer-encapsulated Au nanoparticles were deposited easily in the pores of the mesoporous support, with a high distribution and without aggregation or any modifications in the cluster size, as demonstrated in the high-resolution transmission electron microscopy (HR-TEM) images (Supplementary Fig. S1)[25]. The deposition and anchoring, of the dendrimer-encapsulated Au clusters on the mesoporous support, results from the hydrogen bonding between the OH-terminated PAMAM G4OH dendrimer and the surface of the SiO$_2$ support[25,26]. This interaction prevented the detachment of dendrimer-encapsulated Au clusters from the mesoporous SiO$_2$ support, even under liquid-phase reaction conditions. HR-TEM and X-ray photoelectron

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Table 1 | Cyclopropane synthesis catalysed by 2.0 ± 0.3 nm Au-G4OH/SBA-15.

Entry	Solvent	Temperature (°C)	Selectivity (cis/trans-2:aldehyde 3) (%:%)*	Diasteroselectivity (cis-2:trans-2)[†]	Au in solution (ppm)[‡]
1	MeNO$_2$	70	75:25	8:1	38.2
2	MeNO$_2$	r.t.	100:0	15:1	12.4
3	Toluene	70	55:45	8:1	0.2
4	Toluene	r.t.	97:3	17:1	<0.1

*3 mol% of catalyst and 9 mol% of PhICl$_2$ were used. Selectivity and diastereoselectivity were measured after 12 hours, with full conversion (>99%) of the reactants. The product ratio was analysed by GC. [†]Based on ^{1}H NMR integration. [‡]Based on ICP-MS measurements. Piv = (CH$_3$)$_3$CCO.

spectroscopy (XPS) measurements indicated that there was no change in cluster size and oxidation state of the metal after the deposition of dendrimer-encapsulated Au clusters on the mesoporous SiO$_2$ support.
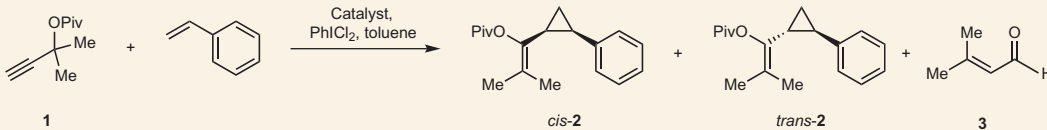
The catalytic activity of Au-G4OH/SBA-15 was first tested for cyclopropanation reactions using propargyl pivalate **1** and styrene as reactants for the formation of *cis*- and *trans*-diastereomers of cyclopropane **2** at 70 °C (ref. 27). After the addition of PhICl$_2$ to the reaction mixture, we observed a high catalytic reactivity of the catalyst with more than 99% conversion within 12 hours (Table 1, entries 1 and 3), along with significant amounts of 3-methyl-2-butenal (**3**). A decrease in the reaction temperature from 70 °C to room temperature (r.t., Table 1, entries 2 and 4) minimized the formation of the undesired aldehyde product **3**. Also, the diastereoselectivity of **2** was improved by a factor of two. Comparison of cluster morphology before and after the reaction showed only minor changes in cluster size (Supplementary Fig. S1).

XPS measurements indicated that, with the addition of PhICl$_2$, Au nanoparticles were oxidized to Au(III) species that interacted with chloride (Supplementary Fig. S2). This observation is consistent with previous *in-situ* XAS measurements of dendrimer-encapsulated Pt nanoparticles loaded on a mesoporous SiO$_2$ support (Pt-G4OH/SBA-15), which indicated that the most-active catalyst for π-bond activation reactions is the highly oxidized Pt(IV) species generated by the oxidation of Pt nanoparticles[21].

The effect of solvent polarity on catalyst stability and leaching-resistance properties was examined. We found that the amount of leached Au species correlated with the solvent polarity and reduced with lower reaction temperatures in a given solvent system. Accordingly, no leaching of Au ions to the solution phase was detected by inductively coupled plasma–mass spectrometry

(ICP-MS) measurements, up to the instrument's detection limit (0.1 ppm), when toluene was employed as the solvent at r.t. (Table 1, entry 4). In contrast, ICP-MS analyses found that 16% of the Au atoms in the catalyst leached to the solution phase when the reaction was conducted in the considerably more-polar solvent nitromethane (Table 1, entry 2). The resulting mixture of homogeneous (Au ions) and heterogeneous (Au-G4OH/SBA-15) catalytically active species produced an enhanced reaction rate, but a deteriorated *cis*:*trans* ratio for **2**. The disparity in reactivity and diastereoselectivity between toluene and nitromethane can be explained by solvent–catalyst interactions: when toluene, a nonpolar solvent, was used in combination with a hydrophilic solid phase (the mesoporous SiO$_2$, the dendrimer matrix and the metal ions), the hydrophobic–hydrophilic repulsions prevented the diffusion of Au ions from the support into the solution phase. By substituting toluene with a more hydrophilic solvent (such as MeNO$_2$), the barrier to the diffusion of the Au ions from the solid Au-G4OH/SBA-15 catalyst to the solution phase decreased, and therefore leached Au ions were detected in the solution phase[21].

To gain further insight into the differences between the homogeneous and heterogeneous Au catalysts, their selectivities were compared. When Au-G4OH/SBA-15 was employed, a similar chemoselectivity to that of AuCl$_3$ was observed, but the diastereomeric ratio (*cis*:*trans*) of **2** increased by fivefold (Table 2, entries 1 and 2, respectively). Previously, it was postulated that the interaction of the olefin substituent with the metal catalyst disfavours the formation of *trans*-cyclopropane[27]. Therefore, we hypothesized that, with a heterogeneous catalyst, the support produces enhanced steric effects around the Au centres, which result in the observed improvement in diastereoselectivity. To test this hypothesis we prepared Au

Table 2 | Homogeneous and heterogeneous Au catalysts for the formation of cyclopropane 2.

Entry	Catalyst*	Conversion (%)	Selectivity (cis/trans-2: aldehyde 3) (%:%)[†]	Diastereoselectivity (cis-2:trans-2)[‡]	Au in solution (ppm)[§]
1	2.0±0.3 nm Au-G40H/SBA-15[‖]	>99	95:5	17:1	0.1
2	AuCl$_3$	>99	95:5	3.5:1	80
3	2.2±0.4 nm Au-PAG4/SBA-15[‖]	>99	93:7	6:1	0.1
4	2.1 + 0.3 nm Au@OA/SBA-15[‖]	>99	80:20	4:1	15
5	AuCl$_3$@G4/SBA-15[¶]	5	93:7	17:1	0.8
6	2.0±0.3 nm Au-G40H/SBA-15 (flow)[#]	58	100:0	18:1	NA**
7	2.1 + 0.3 nm Au@OA/SBA-15 (flow)[#]	>99	87:13	3.5:1	NA**

*2 mol% of catalyst loading was used, with toluene as a solvent at r.t. Conversion, selectivity and diastereoselectivity were measured after 12 hours. [†]Determined by GC. [‡]Determined by ^{1}H NMR integration. [§]Based on ICP-MS measurements. [‖]6 mol% of PhICl$_2$ was added to the reaction. [¶]HAuCl$_4$ was mixed with G4OH/SBA-15, without reduction. [#]Flow rate was 2 ml h^{-1}, reactants and PhICl$_2$ concentrations were 10 mM and 1 mM, respectively. **SiO$_2$-based scavenger was used to prevent the flow of metal ions to the GC.
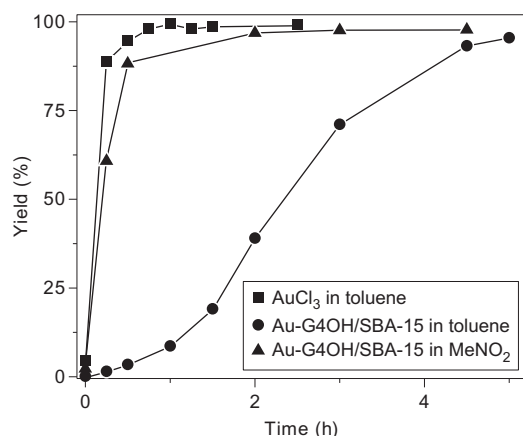
Figure 1 | Batch measurements of cyclopropane 2 yield as function of reaction time at r.t. AuCl$_3$ (filled squares) was used as a homogeneous catalyst in toluene. 2.0 $\pm$ 0.3 nm Au-G4OH/SBA-15 was tested as a heterogeneous catalyst in toluene (filled circles) and MeNO$_2$ (filled triangles). 2 mol% of heterogeneous catalyst were used and 6 mol% of PhICl$_2$ were added to oxidize the metallic clusters. A switch from toluene to MeNO$_2$ increased the solvent's polarity and changed the catalytic rate of the heterogeneous catalyst. The reaction rate with the Au-G4OH/SBA-15 catalyst in MeNO$_2$ is similar to that with AuCl$_3$ due to leaching of Au ions into the solution phase. The leaching of Au ions can be diminished if a less-polar solvent, such as toluene, is employed in this reaction.

nanoparticles encapsulated by two different dendrimers and compared the effect of the dendrimer's properties on the diastereoselectivity of the cyclopropanation reaction. Thus, phenylalanine-terminated G4 (PAG4) dendrimer, with a structure less crowded than that of the PAMAM G4OH dendrimer, was synthesized (Supplementary Scheme S1) as a matrix for Au clusters. As a consequence, the diastereomeric ratio of **2** reduced to 6:1 when the Au-PAG4/SBA-15 catalyst was used, presumably because of the lower packing density of the dendrimer (Table 2, entry 3). Importantly, the average diameter of the Au clusters in the Au-PAG4 catalyst was similar to that in Au-G4OH (2.2 $\pm$ 0.4 and 2.0 $\pm$ 0.3 nm, respectively). Therefore, the changes in the diastereoselectivity most probably correlate to differences in dendrimer properties rather than to differences in cluster size. These results demonstrate the potential to control diastereoselectivity with a heterogeneous catalyst by modification of the matrix in which the clusters are encapsulated.

The differences in the nature of the catalyst (homogeneous versus heterogeneous) manifested in the reaction kinetics (Fig. 1). Using AuCl$_3$ and Au-G4OH/SBA-15 as catalysts, the conversion to **2** was completed after 30 minutes and five hours, respectively. The differences in the properties of the homogeneous and heterogeneous catalysts also affect the shape of the curve when plotting conversion against reaction time. An S-shaped curve was obtained when Au-G4OH/SBA-15 was employed as a catalyst, because of the induction period during which the Au clusters were oxidized to the catalytically active Au(III) species. Interestingly, Au-G4OH/SBA-15 employed in MeNO$_2$ instead of in toluene resulted in a total conversion after less than two hours (Fig. 1). Moreover, in this case, the S-shaped curve was not observed, and the shape of the curve resembled that of the homogeneous catalyst. This result is consistent with our observation of Au leaching (Table 1, entry 2) when the less-hydrophobic MeNO$_2$ is used as a solvent. High reproducibility was obtained in these kinetic measurements, with up to $\pm$5% differences in the measured yield values.

To explore further the effects of the solid-phase matrix on the catalyst properties, 2.1 $\pm$ 0.3 nm Au clusters encapsulated with oleylamine (OA), a non-dendritic capping molecule[28], were synthesized

and tested as a heterogeneous catalyst for the cyclopropanation reaction. When 2.1 $\pm$ 0.3 nm Au@OA/SBA-15 (with the addition of PhICl$_2$ as oxidizer) was used as catalyst, the *cis:trans* ratio of **2** was 4:1 and 20% of the Au atoms in the clusters leached to the solution phase (Table 2, entry 4). As observed earlier, the formation of homogeneous, catalytically active species led to low diastereoselectivity. Moreover, kinetic measurements showed that the reaction rate of cyclopropane formation with 2.1 $\pm$ 0.3 nm Au@OA/SBA-15 was identical to that with AuCl$_3$ (Supplementary Fig. S3). Given this similarity of diastereoselectivity and kinetic behaviour, it can be concluded that with the Au@OA/SBA-15 clusters, the Au ions in the solution phase were the active catalysts and produced the majority of the products.

The recyclability of the two heterogeneous catalysts, Au-G4OH/SBA-15 and Au@OA/SBA-15, was also investigated. No deactivation or changes in the diastereoselectivity were observed during recycling of the Au-G4OH/SBA-15 catalyst up to three times. However, small changes in the induction period were observed, with shorter times needed to oxidize and activate the catalyst after recycling. In stark contrast, when a fresh batch of Au@OA/SBA-15 catalyst was employed, complete conversion was measured after 30 minutes; however, after three recycles of the catalyst, the conversion after 30 minutes was only 25% (Supplementary Fig. S4)[20]. Not unexpectedly, the difference in the recyclability of these two catalysts correlates directly to their leaching-resistance properties.

After investigating the capping effects on the catalytic activity and diastereoselectivity, we sought to gain insights into the nature of the Au clusters. No difference in the product diastereoselectivity was detected when the dendrimer-encapsulated Au cluster size was increased from 2.0 $\pm$ 0.3 nm to 3.1 $\pm$ 0.4 nm with encapsulation in G4 and G5 dendrimer matrices, respectively (Supplementary Fig. S1). However, slower reaction rates and longer induction periods occurred with increasing cluster size, caused by a slower oxidation of the Au clusters and decreased diffusion rates brought about by the more-crowded G5 dendrimer (Supplementary Fig. S5).

To elucidate the nature of the active Au species coordination in the dendrimer-encapsulated cluster, we compared the catalytic reactivity of 2.0 $\pm$ 0.3 nm Au-G4OH/SBA-15 to that of dendrimer-encapsulated Au ions. Although the diastereoselectivity of the Au^{3+}@G4OH/SBA-15 catalyst was high, with a *cis:trans* ratio of 17:1 for **2**, only 5% of the starting material was consumed after 12 hours (Table 2, entry 5). Similar results were found with the addition of 6 mol% PhICl$_2$ to the reaction mixture. The reason for the low reactivity is probably the strong interaction between the metal ions and the amine groups in the PAMAM dendrimer[29], which inhibits the catalytic activity of the Au^{3+} ions. Therefore, to prepare highly active metal ions inside the dendrimer, the Au^{3+} ions must be reduced to the form of Au(0) nanoparticles and then re-oxidized with PhICl$_2$. As a result of this procedure, the Au(III) species are coordinated primarily to chloride ions and not coordinatively saturated by the amine groups in the dendrimer (Supplementary Fig. S2).

Flow-reactor studies. To take full advantage of the heterogeneous nature, and high catalytic activity and selectivity of the dendrimer-encapsulated Au nanoclusters, we also tested them in a flow reactor. Importantly, the high yield and diastereoselectivity of the Au-G4OH/SBA-15 catalyst was maintained when the catalytic reaction was transferred from the batch to the flow mode. For example, using 2.0 $\pm$ 0.3 nm Au-G4OH/SBA-15 as the catalyst in a fixed-bed plug flow reactor[19], in a given injection the maximum yield of cyclopropane **2** was 58% with a *cis:trans* ratio of 18:1 (Table 2, entry 6). The catalyst was deactivated after six hours through the reduction of the oxidized Au clusters back to their
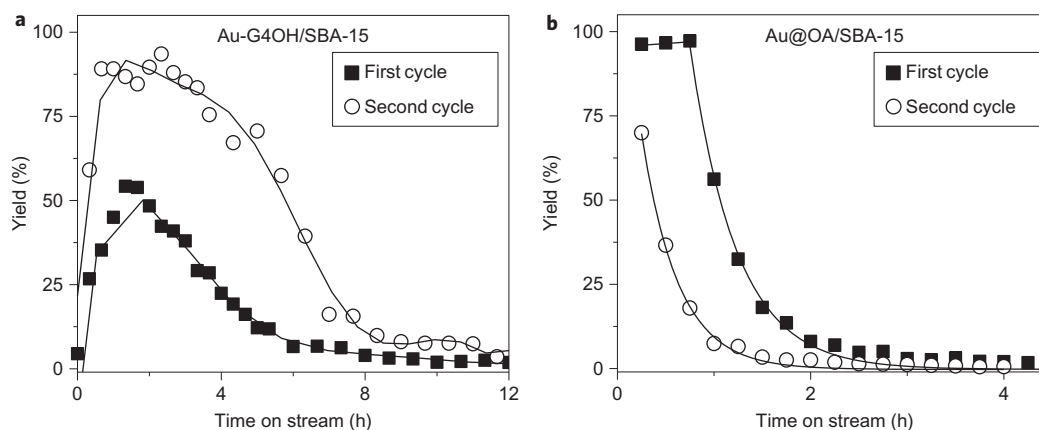
Figure 2 | Flow measurements of cyclopropane 2 yield as function of time on-stream. a,b, 2.0 ± 0.3 nm Au-G4OH/SBA-15 (**a**) and 2.1 ± 0.3 nm Au@OA/SBA-15 (**b**) used as catalysts at r.t. The reactants and oxidizer concentrations in the solution were 0.08 and 0.008 M, respectively. During the first cycle of the reaction (filled squares), Au-G4OH/SBA-15 and Au@OA/SBA-15 were deactivated after six and two hours, respectively. Following oxidation of the two catalysts using a solution of 0.01 M PhICl₂, the catalytic reactivity was measured (open circles). In this cycle, both the yield and the duration of catalytic reactivity of Au-G4OH/SBA-15 were higher than those of Au@OA/SBA-15.

metallic state (Fig. 2a); however, the active catalyst could be regenerated by a flow of $PhICl_2$ (0.05 mmol). Using the regenerated catalysts, the conversion was increased to 90% and the catalyst stayed active for nine hours, until the eventual deactivation (Fig. 2a). This result can be explained by the insights garnered from previous XAS studies[21]. Namely, the percentage of highly oxidized metal ions increased considerably with re-oxidation of the dendrimer-encapsulated metal nanoparticles, which produced the observed increase in reactivity. The enhancement in the catalytic yield and activity after re-oxidation of the catalyst proves the reversibility of the active oxidation state of the metal without any leaching of Au ions to the solution phase (which would cause a decrease in the catalytic yield). In addition, the high diastereoselectivity of the Au-G4OH/SBA-15 catalysts in the batch mode can be maintained in the flow system, which further highlights the truly heterogeneous nature of the dendrimer-encapsulated Au clusters. In contrast to Au-G4OH/SBA-15, a high initial reactivity was measured for Au@OA/SBA-15 in the flow reactor. However, a total deactivation was detected after two hours (Fig. 2b) and a low cyclopropane **2** *cis:trans* ratio of 3.5:1 was measured (Table 2, entry 7). Moreover, both the catalyst activity and the duration of high activity decreased as the catalyst was reused (Fig. 2b). These results demonstrate clearly the superior stability and leaching-resistance properties of Au-G4OH/SBA-15.

Secondary reactions. In the section above we demonstrate that diastereoselectivity in cyclopropanation can be controlled by tuning the matrix properties of the heterogeneous catalyst, which is similar to the role of ligand size in the homogeneous catalyst. Additionally, it is also well known that ligands can have a profound impact on chemoselectivity in homogeneous catalysts. As an alternative strategy, we envisioned that chemoselectivity could be achieved with the heterogeneous system by modifying the residence time of the reactants in a flow reactor[30]. For example, in a cascade reaction pathway, it is conceivable that an intermediate can be selectively trapped by shortening the residence time to prevent further rearrangements. Conversely, it may be possible to maximize the yield of the final rearrangement product by increasing the residence time. Although the effect of the residence time on reaction conversion has been studied previously[31–33], its effect on chemoselectivity is underexploited in preparative synthetic chemistry[34]. Above all, the aforementioned method of tuning chemoselectivity would be an advantage untenable in a batch reaction mode as well as in traditional homogeneous catalysis. Therefore, the highly stereoselective Au-G4OH/SBA-15 catalyst was employed for the sequential cyclopropanation rearrangement of propargyl pivalate **1** and enyne **4**. In this reaction, the primary product, *cis*-cyclopropane **5**, is reported to rearrange catalytically into two secondary products, styrene **6** and fluorene **7** (ref. 35). When using the homogeneous

Table 3 | Gold-catalysed cascade cyclopropanation rearrangement.

Entry	Catalyst	Total conversion (%)	Cyclopropane 5 (%) (*cis*-5:*trans*-5)	Secondary products (%) (6:7)
1	AuCl₃*	50	40 (3:1)	10 (3:2)
2	2.0 ± 0.3 nm Au-G4OH batch mode*,†	40	38 (12:1)	2 (1:1)
3	2.0 ± 0.3 nm Au-G4OH flow mode (5 ml h⁻¹)‡	20	18 (100:0)	2 (100:0)
4	2.0 ± 0.3 nm Au-G4OH flow mode (0.1 ml h⁻¹)‡	72	0	72 (100:0)

Reaction yield and selectivity were measured by ¹H NMR integration. *Reaction run for 20 hours at r.t. with 2 mol% catalyst. †6 mol% oxidizer was added. ‡Total yield and selectivity were measured after four hours of reactant flow at r.t. Reactant and oxidizer concentrations were 0.15 and 0.015 M, respectively.
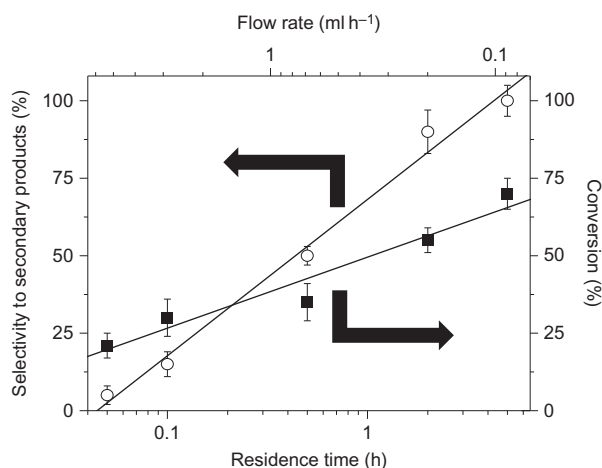
Figure 3 | Flow measurements of the conversion and selectivity of the cascade cyclopropanation-rearrangement reaction as a function of reactant residence time. With 2.0 ± 0.3 nm Au-G4OH/SBA-15 as the catalyst, the catalytic conversion (filled squares) and selectivity (open circles) towards the formation of secondary products **6** and **7** at r.t. increased as a function of the residence time of the reactants. The reactant and oxidizer concentrations were 0.15 and 0.015 M, respectively. Error bars represent up to $\pm 6\%$ differences in reproducibility.

AuCl$_3$ catalyst at r.t., a 40% yield of cyclopropane **5** was obtained, with a *cis:trans* ratio of 3:1, accompanied by a 10% yield of products **6** and **7** (in a 3:2 ratio) formed by the rearrangement of the product *cis*-**5** (Table 3, entry 1). Switching to the heterogeneous Au-G4OH/SBA-15 catalyst in the batch mode led to a considerably better selectivity, with a *cis:trans* ratio of 12:1 for **5** and only a small amount of the rearrangement products **6** and **7** (1% each) (Table 3, entry 2). Subsequently, the same catalyst was employed in the flow mode. This set-up led to the discovery of an interesting correlation of product distribution with the reactant's residence time. With a flow rate of 5 ml h^{-1}, an 18% yield of *cis*-cyclopropane **5** was measured (*cis:trans* ratio of 100:0), along with 2% of secondary products **6** and **7** (Table 3, entry 3). Moreover, the selectivity of the rearrangement products **6** and **7** also changed when using the flow system. Although in the batch mode the product ratio **6**:**7** was 1:1, in the flow mode, product **6** formed exclusively. By reducing the flow rate to 0.1 ml h^{-1} and thereby increasing the residence time, the conversion increased by more than threefold to 72% and an exclusive selectivity for the rearrangement product **6** was obtained (Table 3, entry 4).

By continuously changing the residence time of the reactants we were able to demonstrate a linear increase in the reactivity coupled with a linear enhancement in the selectivity towards the rearrangement product **6** (Fig. 3). Clearly, in this reaction the reactant residence time played an important role in achieving better selectivity and reactivity with the heterogeneous catalyst. These results are highly significant because, although the use of flow reactors for catalytic reactions is employed widely for a variety of homogeneous reactions[30,31], few examples show that the product selectivity can be changed by tuning the residence time of the reactants[34].

Conclusions

A highly diastereoselective and chemoselective heterogeneous Au catalyst for cyclopropanation reactions was developed. The dendrimer-encapsulated heterogeneous Au catalyst, Au-G4OH/SBA-15, was activated through metal oxidation by PhICl$_2$. When employed in toluene for the cyclopropanation reaction of propargyl pivalate **1** and styrene, the *cis:trans* ratio of the cyclopropane **2** was enhanced by fivefold compared to that of the homogeneous AuCl$_3$-catalysed

transformation. In addition to the conventional batch-mode reaction, Au-G4OH/SBA-15 and Au@OA/SBA-15 were both loaded onto a fixed-bed plug flow reactor. With Au-G4OH/SBA-15, the reactivity, diastereoselectivity and catalyst lifetime were superior. Significantly, after the initial deactivation the Au-G4OH/SBA-15 catalyst can be regenerated by a catalyst re-oxidation using PhICl$_2$. Interestingly, the regenerated catalyst possesses an even higher reactivity and a longer lifetime, and maintains a high diastereoselectivity. Also, the heterogeneous Au-G4OH/SBA-15 catalyst was employed for the sequential cyclopropanation-rearrangement reaction of propargyl pivalate **1** and enyne **4**, and again demonstrated an enhancement in diastereoselectivity compared to that with AuCl$_3$. The truly heterogeneous nature of Au-G4OH/SBA-15 allows the tuning of product distribution by modifying the flow parameters. By increasing the residence time of the reactants, both the reactivity and the selectivity towards the formation of the secondary products **6** and **7** were enhanced. These results demonstrate compellingly the potential advantages of heterogenizing homogeneous catalysts and serve to highlight the means to control reactivity and stereoselectivity unique to heterogeneous catalysts.

Methods

Au nanoparticles synthesis. G4 PAMAM dendrimer (G4OH) (Dendritech) stock solution (250 μM) was prepared by adding water and diluting to 51.6 ml in a 100 ml round-bottomed flask. The flask was purged with Ar for 30 minutes and sealed tightly with a septum. 0.01 M HAuCl$_4$ (6 ml) was then added into the flask dropwise with vigorous stirring. Immediately afterwards, a 20-fold excess of a freshly prepared mixture of 0.5 M NaBH$_4$ and 0.15 M NaOH (stored at 0 °C before use) was injected dropwise into the flask with vigorous stirring[23]. The reaction solution was then stirred for three hours, after which the solution (60 ml) was purified by dialysis against two litres of deionized water in cellulose dialysis sacks. Dialysis occurred over 24 hours with the water changed four times.

Mesoporous SBA-15. Mesoporous SBA-15 silica was prepared utilizing a conventional method[24].

Supported nanoparticles. Au nanoparticles were loaded onto the mesoporous SBA-15 silica prior to the catalytic studies. SBA-15 was added to a colloidal solution of the Au-G4OH or Au@OA nanoparticles and the resulting slurry was sonicated for three hours at r.t. The nanoparticle-supported SBA-15 was separated from the solution by centrifuge at 4,200 revolutions per minute (r.p.m.) for six minutes. After centrifugation, the solution became clear. The solution was then decanted and the catalyst was dried at 100 °C overnight. The loading of Au was determined by ICP-MS.

Au^{3+}@G4OH/SBA-15. 250 μmol G4OH dendrimer solution was mixed with 200 mg of SBA-15 in 30 ml of H$_2$O for three hours. The G4OH/SBA-15 was separated from the solvent by centrifuge at 4,200 r.p.m. for ten minutes. 0.01 mmol HAuCl$_4$ was mixed with G4OH/SBA-15 in 30 ml of H$_2$O for two hours. The Au^{3+}@G4OH/SBA-15 solid was separated from the solvent by centrifugation. The solution was then decanted and the catalyst dried at 100 °C overnight. The loading of Au was determined by ICP-MS.

Representative procedure for catalytic reactions in a batch reactor. Prior to the addition of all other reaction materials, the catalyst Au-G4OH/SBA-15 (1 wt/wt% Au, 50 mg, 0.0025 mmol Au) was put into an oven-dried 10 ml Schlenk tube with a stir bar and placed under 1 atm of H$_2$. The catalyst was then heated to 100 °C for 24 hours and afterwards the H$_2$ atmosphere was replaced with N$_2$. For the cyclopropane formation a mixture of styrene (40 μl, 0.25 mmol), propargyl pivalate **1** (10 mg, 0.15 mmol), PhICl$_2$ (1.9 mg, 0.007 mmol), PhMe$_6$ (2 mg, 0.012 mmol, internal standard) and toluene-d_8 (1.5 ml) was made. For the cyclopropane-rearrangement reaction, a mixture of enyne **4** (15 mg, 0.105 mmol), propargyl pivalate **1** (15 mg, 0.089 mmol), PhICl$_2$ (1.9 mg, 0.0070 mmol), PhMe$_6$ (2 mg, 0.012 mmol, internal standard) and toluene-d_8 (2 ml) was prepared. The reaction mixture was added to the Schlenk tube and degassed (by freeze–pump–thaw) three times before back-filling with 1 atm of N$_2$. The Schlenk tube was sealed and the mixture stirred at the specified temperature. After the reaction, the solid catalyst was filtered through a glass microfibre filter (Whatman GF-H). The filtrate was analysed by ^{1}H NMR spectroscopy.

Flow reactor. The Au-G4OH/SBA-15 and Au@OA/SBA-15 catalysts (200–300 mg, 1 wt/wt%) were reduced at 100 °C for 24 hours under 1 atm of H$_2$. Afterwards, the catalysts were packed in a 50 mm long HPLC column (internal diameter, 5 mm). The catalyst was treated first with a solution of 0.05 mmol PhICl$_2$ in 10 ml toluene, which was pumped through the reactor at a flow rate of 1 ml h^{-1}. Also, a solution of 0.25 mmol PhICl$_2$, 1 mmol PhMe$_6$, 2.5 mmol styrene and 2.5 mmol propargyl pivalate **1** in 30 ml of toluene was prepared. This mixture was pumped through the

reactor at a flow rate of 1 ml h^{-1}. For the rearrangement reaction, 0.05 mmol of PhICl$_2$, 0.5 mmol of PhMe$_6$, 0.5 mmol of enyne **4** and 0.5 mmol of propargyl pivalate **1** were dissolved in 30 ml of toluene. This solution was pumped through the reactor at flow rates between 0.01 ml h^{-1} and 5 ml h^{-1}. The conversion and product yield were monitored by gas chromatography (GC, gas chromatograph HP5890II equipped with a 30 m HP-5 capillary column) and by ^{1}H NMR spectroscopy.

Elemental analysis by ICP-MS. After the reaction period was over, the reaction mixture was filtered through a glass microfibre filter (Whatman GF-H), and both the supernatant and solid catalysts were collected. The Au catalyst was mixed with aqua regia (concentrated HCl:concentrated HNO$_3$ = 3:1, 1 ml) solution for 10 hours. After the Au-containing species had dissolved, the residual white solid (SBA-15) was filtered and the acidic solution mixed with 6 ml of H$_2$O and analysed by ICP-MS. To analyse the filtrate by ICP-MS, toluene was evaporated under reduced pressure and the remaining solids were dissolved in 1 ml aqua regia and 6 ml H$_2$O. This solution was also analysed by ICP-MS.

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Author contributions

E.G. and J.H.L. performed the experiments and synthesized materials, substrates and catalysts. F.D.T. and G.A.S. supervised the research. All authors contributed to the conception of the experiments, discussed the results and commented on the manuscript.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permission information is available online at http://www.nature.com/reprints. Correspondence and requests for materials should be addressed to F.D.T. and G.A.S.

Competing financial interests

The authors declare no competing financial interests.