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ARTICLE

Mechanistic examination of Au^{III}-mediated 1,5-enyne cycloisomerization by AuBr₂(*N*-imidate)(NHC) / AgX precatalysts – is the active catalyst Au^{III} or Au^I?

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Gold(III) catalysts mediate 1,5-enyne cycloisomerization or tandem nucleophilic substitution-1,5-enyne cycloisomerization processes in an efficient manner. This study examines the reaction kinetics of 1,5-enyne cycloisomerization, mediated by AuBr₂(*N*-imidate)(NHC) catalysts {where *N*-imidate = *N*-tetrafluorosuccinimide (*N*-TFS) or *N*-phthalimide (*N*-phthal) and NHC = *N,N'*-di-*tert*-pentylimidazol-2-ylidene (*I*^tPe)}, in the presence of AgOTf, in comparison with Au^{III}Br₃(NHC) and Au^IBr(NHC). The nature of *N*-imidate anion influences catalyst efficacy. NMR spectroscopic investigations have allowed the ease of reduction of AuBr₂(*N*-TFS)(NHC) to Au^IX(NHC) (where X = *N*-TFS or Br) to be examined. Br₂ is liberated from Au^{III}, which has been trapped by a sacrificial alkene. Under working catalyst conditions cationic Au^{III} is reduced to Au^I.

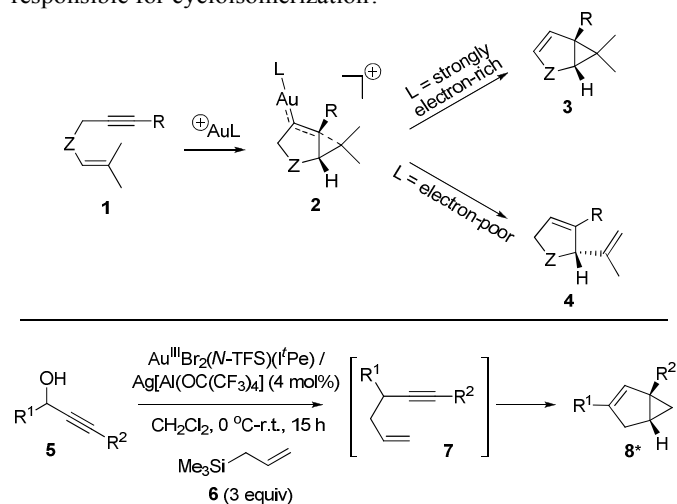
Introduction

Organic transformations catalysed by Au species are of current interest within both the synthetic chemistry and catalysis communities.¹ Of the reaction classes, 1,*n*-enyne cycloisomerization processes (*n* = 5 and 6) have attracted notable attention.² While several transition metals are able to affect 1,*n*-enyne substrates, Au occupies a special position in this arena,^{2,3} as an eclectic array of structurally diverse organic products can be formed, depending on the catalyst and substrate identities, in addition to the reaction conditions used.

1,6-Enyne cycloisomerization processes generally involve 6-*exo*-dig cyclization and are mechanistically well understood.⁴ 1,5-Enyne cycloisomerization processes, involving 5-*endo*-dig cyclization, have not been examined to the same extent, despite the numerous synthetic possibilities. Nevertheless, several catalyst manifolds are known to deliver different products depending on the electronic character of the Au centre (see Scheme 1 for selected examples). This prompted Sun and Lee to explore the mechanisms of 1,5-enyne cycloisomerization, mediated by Au^I, by DFT calculations (B3LYP).⁵

In an earlier study we developed a tandem nucleophilic substitution-1,5-enyne cycloisomerization process (5→8),⁶ starting from propargyl alcohol (5) and allyl silane (6) starting materials, to deliver bicyclo[3.1.0]hexene products (8). For this process, Au^{III}Br₂(*N*-TFS)(*I*^tPe) in combination with the non-coordinating anion, Ag[Al(OC(CF₃)₄)]₄, proved an active and selective catalyst for the tandem process. By comparison with Au^IBr(*I*^tPe) (note: near-inactive for the tandem process), it was shown that a Au^{III} species was required for the initial nucleophilic substitution reaction. However, a question that arose from the study was the nature of the active catalyst

species in the cycloisomerization step, *i.e.* is Au^{III}- or Au^I responsible for cycloisomerization?



Scheme 1. Top: 1,5-enyne cycloisomerization showing how L can direct selectivity (3 & 4 representative products; others possible). Bottom: a tandem nucleophilic substitution-1,5-enyne cycloisomerization – thermal 1,3-rearrangements are possible for 8 (R¹/R² = aryl groups).

In this paper we examine the reaction kinetics of 1,5-enyne cycloisomerization, mediated by AuBr₂(*N*-imidate)(NHC) catalysts {where *N*-imidate = *N*-tetrafluorosuccinimide (*N*-TFS) or *N*-phthalimide (*N*-phthal) and NHC = *N,N'*-di-*tert*-pentylimidazol-2-ylidene (*I*^tPe)} in the presence of AgOTf. The findings allow an understanding of 1,5-enyne substrate

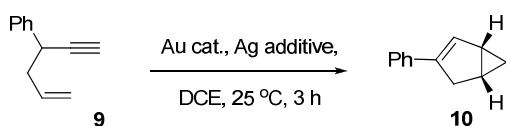
turnover, indicating that catalyst decomposition is an issue for certain catalysts. It has been found that the *N*-imidate anion plays a stabilizing role for effective catalysis. NMR spectroscopic investigations have been used to examine the degradation of Au^{III} to Au^I, which support the kinetic studies.

Results and discussion

The study is divided into two parts: (a) kinetic investigations; (b) NMR spectroscopic investigations.

(a) Kinetic investigations

The 1,5-enyne cycloisomerization reaction (**9**→**10**) examined in these kinetic investigations is shown in Scheme 2, which has previously been validated as a useful benchmark reaction^{6b} for testing Au catalyst efficacy (the reaction is selective for **10** and negligible side-reactions are seen).



Scheme 2. 1,5-Enyne cycloisomerization reaction for the kinetic investigations.

The catalysts used in this study are collated in Figure 1, which were selected from a wider library of catalysts previously reported by our group.^{6a,b}

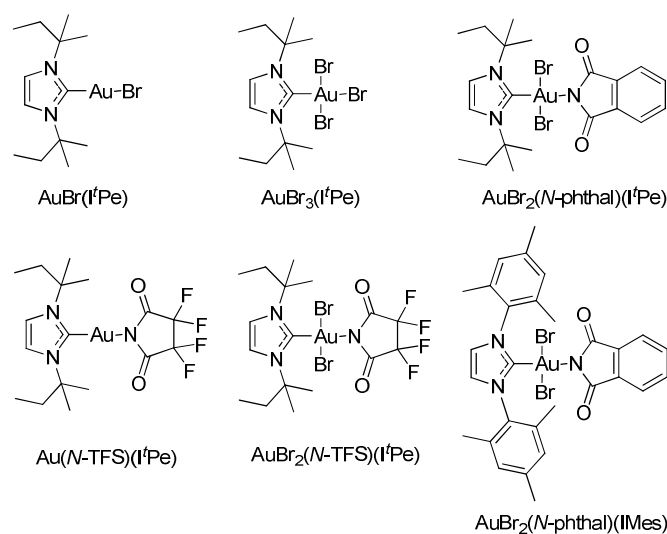


Figure 1. The structures of the catalysts used in this mechanistic study.

The reaction of **9**→**10** was monitored by HRGC analysis. The response factors are near identical for **9** and **10** (authenticated by ¹H NMR spectroscopic analysis), which is expected as they are isomers. The conversion of pure **9** (ascertained by ¹H NMR spectroscopy, see section b) and associated kinetic profile is shown in Figure 2 for the reaction mediated by 1 mol% AuBr₂(*N*-TFS)(I'Pe), in the presence of either 1 or 2 mol% AgOTf in DCE at 25 °C. The first equivalent (relative to Au

cat.) serves to abstract bromide from AuBr₂(*N*-TFS)(I'Pe) forming [AuBr(*N*-TFS)(I'Pe)]OTf and AgBr *in situ*. The second equivalent of AgOTf could in principle abstract another bromide.

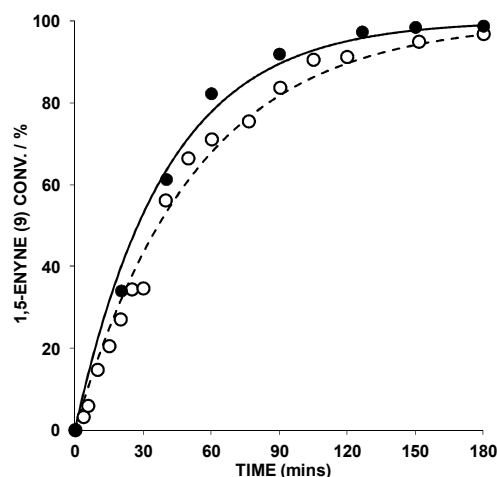


Figure 2. Effect of AgOTf equivalents relative to AuBr₂(*N*-TFS)(I'Pe) in 1,5-enyne cycloisomerisation of **9** (key: ● = 2 mol% AgOTf; ○ = 1 mol% AgOTf). Other details: [**9**] = 0.2 M, DCE, 1 mol% Au cat., 25 °C; 1,5-enyne conversion was monitored by HRGC – each sample point was quenched by addition of *N*(*n*-Bu)₄Br. The kinetic curves were fitted using Dynafit™.

Examination of the kinetic profiles in Figure 2 indicate that there is no benefit in adding an additional equivalent of AgOTf. Both AgOTf and AuBr₂(*N*-TFS)(I'Pe) are necessary for active catalysis (confirmed by control experiments). The data generated by HRGC could be fitted to a pseudo-first order rate equation using Dynafit™ (by curve fitting; regression analysis of ln[enyn] vs time afforded similar data), which allows the observed rate (k_{obs}) and initial rate to be determined.⁷ For the reaction where the AuBr₂(*N*-TFS)(I'Pe):AgOTf was 1:1, it was determined that $k_{\text{obs}} = 3.14 \times 10^{-4} \text{ s}^{-1}$ and the initial rate (T_0) = $6.28 \times 10^{-5} \text{ moldm}^{-3}\text{s}^{-1}$ (standard error = 2.5 %). A marginally faster reaction was recorded when the ratio was 1:2 ($k_{\text{obs}} = 4.16 \times 10^{-4} \text{ s}^{-1}$; $T_0 = 8.32 \times 10^{-5} \text{ moldm}^{-3}\text{s}^{-1}$; standard error = 3.3%).

Based on these data the ratio of the Au catalyst to Ag additive was maintained at 1:1 for all subsequent reactions, which is in-keeping with the ratio commonly used for many related cycloisomerization processes.

The kinetic profiles for the conversion of **9** (by HRGC), catalyzed by five different Au catalysts, are shown in Figure 3. The kinetic data is collated in Table 1. AuBr(I'Pe), AuBr₂(*N*-TFS)(I'Pe), AuBr₂(*N*-phthal)(I'Pe) and AuBr₂(*N*-phthal)(IMes) show reasonable first order behaviour in **9**. The catalyst showing the highest observed rate is AuBr(I'Pe) ($k_{\text{obs}} = 13.98 \times 10^{-4} \text{ s}^{-1}$), which has an initial rate commensurate with AuBr₃(I'Pe) ($T_0 = 27.96 \times 10^{-5} \text{ moldm}^{-3}\text{s}^{-1}$ and 21.87×10^{-5} , respectively). It is important to note that AuBr₃(I'Pe) did not display clean first order behaviour and catalyst deactivation is apparent after *ca.* 60 substrate turnovers. The kinetic profile could, however be fitted to a second order rate equation by

curve-fitting, in which it was assumed that the Au catalyst decomposed over time and that the rate depended on both the concentration of **9** and Au catalyst.

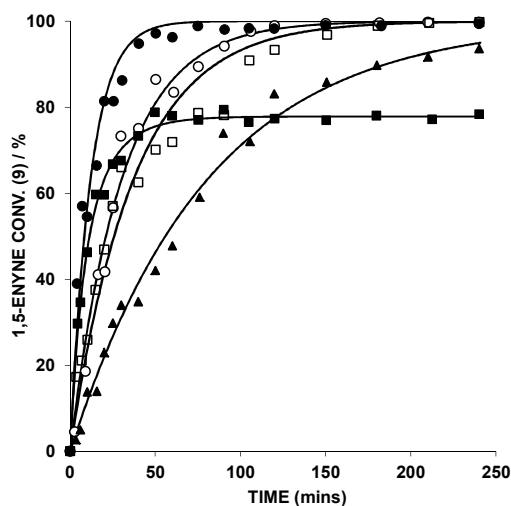


Figure 3. Effect of 1,5-enyne concentration [**9**] on the kinetics in a reaction mediated by various Au catalysts (1 mol%), AgOTf (1 mol%), in DCE at 25 °C (key: closed circles = AuBr(I'Pe); open circles = AuBr₂(N-TFS)(I'Pe); closed squares = AuBr₃(I'Pe); open squares = AuBr₂(N-phthal)(I'Pe); closed triangles = AuBr₂(N-phthal)(IMes)). 1,5-Enyne conversion monitored by HRGC analysis – each sample point was quenched by addition of (*n*-Bu)₄NBr. The kinetic curves were fitted using Dynafit™ with standard errors < 5%.

Table 1. Observed rate constants and initial rates for the cycloisomerization of 4-phenyl-1-hexen-5-yne (**9**) by Au^I and Au^{III} catalysts; data accompanying Figure 3.

Catalyst	$k_{\text{obs}} \times 10^{-4} (\text{s}^{-1})$	Initial Rate ^a	Error (%)
[AuBr(I'Pe)]	13.98	27.96	4.2
[AuBr ₃ (I'Pe)]	^b	21.87	2.3
[AuBr ₂ (N-TFS)(I'Pe)]	5.52	11.04	3.0
[AuBr ₂ (N-phthal)(I'Pe)]	4.49	8.97	4.2
[AuBr ₂ (N-phthal)(IMes)]	2.07	4.14	2.0

^a Rate at $T_0 \times 10^{-5} (\text{mol dm}^{-3} \text{s}^{-1})$. ^b Second order, $k_{1\text{obs}} = 0.5468 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$, $k_{2\text{obs}} = 9.07 \times 10^{-4} \text{ s}^{-1}$ (error 3.0%).

The second order rate equation was deduced from initial rate = $k_{1\text{obs}}[\text{enyn}]_0[\text{Au}]_0 = 21.87 \times 10^{-5} \text{ mol dm}^{-3} \text{ s}^{-1}$, where $k_{1\text{obs}}$ ($0.5468 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$) is the rate constant for the equation: **9** (1,5-enyne) + Au → Au + **10** (product). The rate of catalyst decomposition was determined by initial rate of decomposition = $k_{2\text{obs}}[\text{Au}]_0 = 1.81 \times 10^{-6} \text{ s}^{-1}$, where $k_{2\text{obs}}$ ($9.07 \times 10^{-4} \text{ s}^{-1}$) is the rate constant for the decomposition of the Au active catalyst. The inactive Au is more likely colloidal, as evidenced by the kinetic data and purple colouration of the reaction mixture.

Catalyst decomposition does not appear to hinder catalysis by the other Au^{III} complexes tested in this series. Comparison of k_{obs} for the AuBr₂(N-phthal)(I'Pe) and AuBr₂(N-phthal)(IMes) catalysts, shows that the former is twice as active as the latter (Table 1). AuBr₂(N-TFS)(I'Pe) has a marginally higher activity than AuBr₂(N-phthal)(I'Pe). It is evident that the

N-imidate ligand could be playing a stabilizing role, when comparing N-imidate-containing catalysts directly with AuBr₃(I'Pe).

In the course of these kinetic studies it was determined that 'aged' 1,5-enyne significantly affects the kinetic profiles recorded. Aldehyde decomposition products are formed from **9** (observed by ¹H NMR, *ca.* 5%, after several weeks), which could interfere with the catalysis (*i.e.* slowing catalytic turnover). It was therefore found essential to employ either freshly prepared or purified **9** for the kinetic studies, which gave reproducible kinetic data.

Further examination of the catalytic behaviour of AuBr₂(N-phthal)(I'Pe) by variation of [**9**] reveals an interesting trend (Figure 4, Table 2).

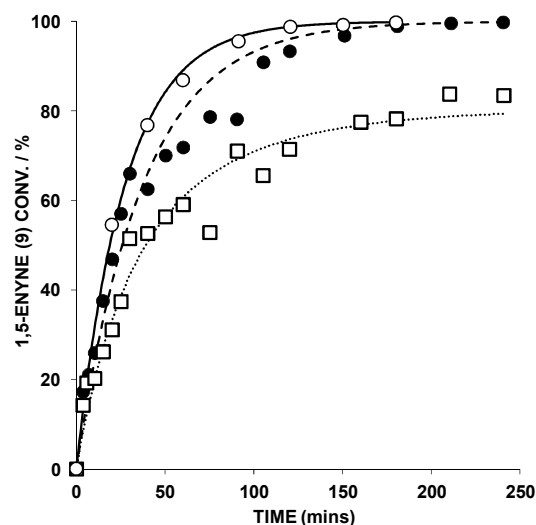


Figure 4. Effect of 1,5-enyne concentration [**9**] in a reaction mediated by AuBr₂(N-phthal)(I'Pe) (1 mol%), AgOTf (1 mol%), in DCE at 25 °C (key: ○ = 0.1 M **9**; ● = 0.2 M **9**; □ = 0.5 M **9**). 1,5-Enyne conversion monitored by GC analysis – each sample point was quenched by addition of (*n*-Bu)₄NBr. The kinetic curves were fitted using Dynafit™.

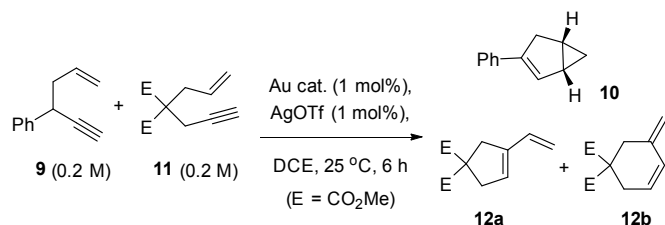
Table 2. Observed rate constants for the cycloisomerization of [**9**] mediated by AuBr₂(N-phthal)(I'Pe); data accompanying Figure 4.

[9] (mol.dm ⁻³)	$k_{\text{obs}} \times 10^{-4} (\text{s}^{-1})$	Initial Rate ^a	Error (%)
0.1	6.15	6.15	1.6
0.2	4.49	8.97	4.2
0.5	^b	19.20	5.7

^a at $T_0 \times 10^{-5} (\text{mol dm}^{-3} \text{ s}^{-1})$. ^b Second order $k_{1\text{obs}} = 7.68 \times 10^{-2} \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$, $k_{2\text{obs}} = 2.36 \times 10^{-4} \text{ s}^{-1}$.

Increasing [**9**] causes a decrease in the observed rate constants, with the initial rates increasing with concentration, relating to the change in [**9**] over time. At 0.5 M [**9**] it was necessary to fit the kinetic curve to a second order rate equation, again factoring in the Au catalyst deactivation step. The observation is consistent with increasing [Au], which is concomitant with increasing [**9**]. Given these data, product inhibition and Au aggregation / decomposition are likely at higher [**9**].

A question arising from these studies is the nature of the active catalyst species. Therefore, a competition experiment was devised to discern any subtle differences in catalyst behaviour. Dimethyl allylpropargylmalonate **11** was selected as a viable 1,6-enyne benchmark substrate, which principally affords the cyclic products **12a** and **12b** (Scheme 3).



Scheme 3. Competition experiment of a 1,5-enyne **9** and 1,6-enyne **11**. Product **11** derives from **9** and products **12a** and **12b** from **11**. The kinetic profiles are shown in Figure 6 and product distributions of **12a:12b** shown in Figure 7.

1,5-Enyne **9** (0.2 M) and 1,6-enyne **11** (0.2 M) were subjected to a reaction where the only variable was the Au catalyst {AuBr(I'Pe), AuBr₂(*N*-TFS)(I'Pe) and AuBr₂(*N*-phthal)(I'Pe)} (Figure 5 and Table 3). In addition to examining the reactivity difference between **9** and **11**, the experiment allows one to probe the ratio of products formed in the latter 1,6-enyne cycloisomerization reaction (**12a:12b**) as the substrate is consumed over time.

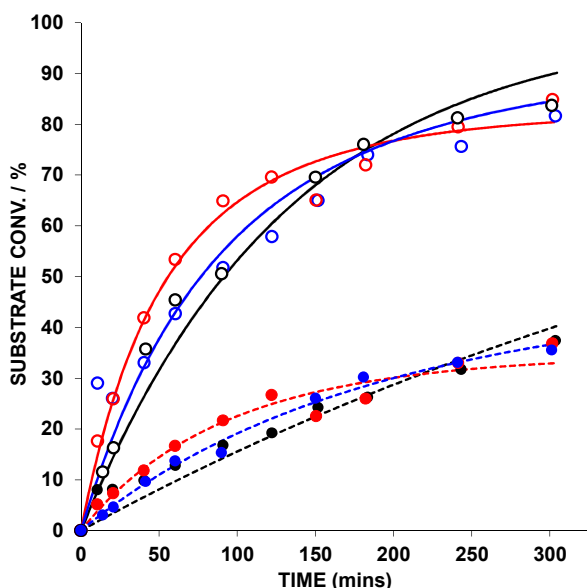


Figure 5. Kinetic profile for the concurrent cycloisomerisation of 4-phenyl-1-hexen-5-yne (**9**) and dimethyl allylpropargylmalonate (**11**) mediated by selected Au catalysts. Key: 1,5-enyne conversion (**9**, open circles) and 1,6-enyne conversion (**11**, closed circles) – black = AuBr(I'Pe); blue = AuBr₂(*N*-TFS)(I'Pe); red = AuBr₂(*N*-phthal)(I'Pe). Conditions: 0.2 M **9**, 0.2 M **11** in 1,2-dichloroethane, 1 mol% Au, 1 mol% AgOTf, 25 °C. 1,*n*-enyne (*n* = 5 or 6) conversion monitored by GC analysis – each sample point was quenched by addition of (*n*-Bu)₄NBr. The kinetic curves were fitted using Dynafit™ with standard errors ~ 5%.

Table 3. Observed rate constants and initial rates for the concurrent cycloisomerization of 1,5-enyne (**9**) and 1,6-enyne (**11**), mediated by selected Au catalysts; data accompanying Figure 5.

Catalyst	$k_{\text{obs}} \times 10^{-4} \text{ (s}^{-1}\text{)}$	Rate ^a	Error (%)	Ratio 12a:12b ^b
1,5-enyne				
AuBr(I'Pe)	1.27	2.53	5.3	-
AuBr ₂ (<i>N</i> -TFS)(I'Pe)	^{c,d}	3.47	2.6	-
AuBr ₂ (<i>N</i> -phthal)(I'Pe)	^{e,f}	5.28	4.2	-
1,6-enyne				
AuBr(I'Pe)	0.28	0.56	8.4	0.28
AuBr(I'Pe)	1.08	2.15	2.2	0.30
(1,6-enyne 11 only)				
AuBr ₂ (<i>N</i> -TFS)(I'Pe)	^{d,g}	0.85	3.8	0.45
AuBr ₂ (<i>N</i> -phthal)(I'Pe)	^{f,h}	1.30	5.6	0.36

^a Rate at $T_0 \times 10^{-5} \text{ (mol dm}^{-3} \text{ s}^{-1}\text{)}$. ^b After 6 h. ^c Second order $k_{1\text{obs}} = 8.685 \times 10^{-2} \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$. ^d $k_{2\text{obs}} = 6.38 \times 10^{-5} \text{ s}^{-1}$ (error 9.2%). ^e Second order $k_{1\text{obs}} = 0.1321 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$. ^f $k_{2\text{obs}} = 1.52 \times 10^{-4} \text{ s}^{-1}$ (error 8.0%). ^g Second order $k_{1\text{obs}} = 2.128 \times 10^{-2} \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$. ^h Second order $k_{1\text{obs}} = 3.242 \times 10^{-2} \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$.

Firstly, AuBr(I'Pe) is a competent catalyst for the cycloisomerization of **11** → **12** ($k_{\text{obs}} = 1.08 \times 10^{-4} \text{ s}^{-1}$; $T_0 = 2.15 \times 10^{-5} \text{ mol dm}^{-3} \text{ s}^{-1}$; standard error = 2.2%). The kinetic analysis of the competition experiments is complicated by the presence of two substrates and two competing catalytic cycles, which is evident in the error analysis. This complication aside, the kinetic profiles are similar in all cases (see Fig. 5). Catalyst performance is reduced for AuBr(I'Pe) as compared to the Au^{III} catalysts – the presence of **12** slows catalytic turnover in the case of AuBr(I'Pe).

A plot of the ratio of **12a:12b** over the duration of the 1,6-enyne cycloisomerization reaction, reveals an interesting trend as a function of catalyst (Figure 6).

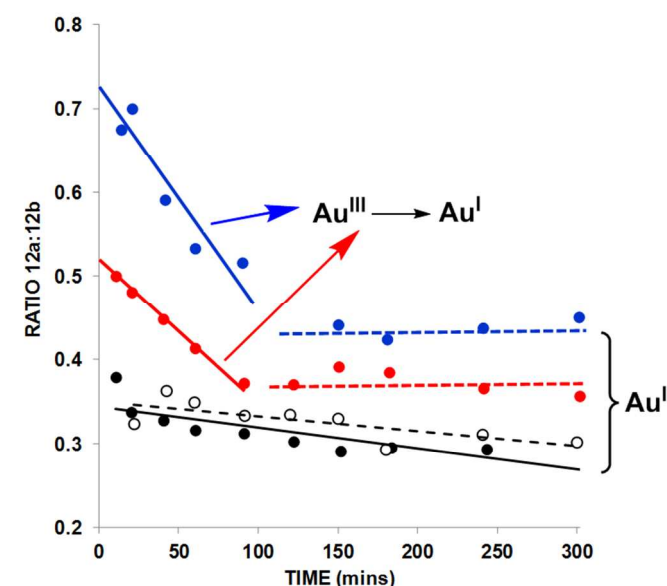


Figure 6. Product distribution from the cycloisomerization of **11** → **12a** and **12b** over time (data extracted from the kinetic profiles given in Figure 5 – closed black circles = AuBr(I'Pe); open black circles = AuBr(I'Pe) / 1,6-enyne **11** only; closed blue circles = AuBr₂(*N*-TFS)(I'Pe); closed red circles = AuBr₂(*N*-phthal)(I'Pe). The trendlines added to the graph serve as a guide to the eye.

Firstly, the independent 1,6-enyne cycloisomerisation of **11**→**12a/12b** mediated by AuBr(I'Pe) gives a ratio of *ca.* 1:3, which does not alter appreciably over the 6 h reaction time. The same trend is revealed in the competition experiment in the presence of both **9** and **12**, using AuBr(I'Pe) as the catalyst. The product distribution is different for the Au^{III} catalysts, with AuBr₂(*N*-TFS)(I'Pe) showing a smaller ratio than AuBr₂(*N*-phthal)(I'Pe). Crucially, at *ca.* 1.5 h the ratio of **12a/12b** is identical to the AuBr(I'Pe) catalyst. This finding, coupled with our previous observation that dual Au^{III}/Au^I catalyst behaviour is necessary for a successful tandem nucleophilic / 1,5-enyne cycloisomerization reaction,^{6a} indicates that Au^{III} to Au^I degradation under the working reaction conditions, affects the ratio of products depending on distribution of Au^{III}/Au^I species that are present at any given time. It may be conjectured that liberated *N*-imidate anion could affect the distribution of **12a/12b** under the reaction conditions. However, in control experiments we have detected liberation of Br₂ from these Au^{III} catalysts (see section b, below).

(b) NMR spectroscopic investigations

NMR spectroscopic analysis allows us to discern whether Au^{III} could be playing a role in the catalysis detailed earlier. It has been suggested previously that Au^{III} can be reduced to Au^I under the reaction conditions.⁸ Nolan and co-workers^{8a} stated that the active catalyst in the hydration of alkynes and polymerisation of styrene mediated by AuBr₃(NHC) type complexes is a Au^I species, formed by reductive elimination of bromide ligands. Further examination of the behaviour of the Au catalysts described herein was deemed necessary, especially whether any evidence for the formation of a cationic Au^{III} catalyst species, and degradation to Au^I, could be gathered.

¹H NMR spectroscopy was used to assess whether cationic Au^{III} species were formed by a stoichiometric reaction of AuBr₂(*N*-TFS)(I'Pe) with AgOTf in acetone-*d*₆ (this solvent was selected to increase solubility of all the salts). The I'Pe imidazole proton signals were the most characteristic and sensitive to changes in the Au electronic configuration. It was necessary to compare NMR spectra with reference materials, namely AuBr(I'Pe) and Au(*N*-TFS)(I'Pe), as shown in Figure 7.

The AuBr(I'Pe) imidazole signal shifts 0.15 ppm downfield on treatment with AgOTf, giving Au(OTf)(I'Pe) quantitatively {compare spectra (h) and (f), Figure 7}. AuBr₂(*N*-TFS)(I'Pe) reacts with AgOTf to afford Au(*N*-TFS)(I'Pe) and trace Au(OTf)(I'Pe), with no cationic Au^{III} species observed after 4.5 h {compare spectra (d), (e) and (i)}. The outcome is consistent with the liberation of Br₂ (as noted by a brown colouration). Furthermore, AuBr₃(I'Pe) decomposes in solution in the absence of AgOTf, leading to the formation of AuBr(I'Pe) {compare spectra (g) and (h)}. Ageing of AuBr₂(*N*-TFS)(I'Pe) led to slow formation of trace but observable amounts of AuBr₃(I'Pe), AuBr(I'Pe) and Au(*N*-TFS)(I'Pe) {see spectrum (b)}. The formation of Au(*N*-TFS)(I'Pe) is detected by 19F NMR spectroscopic analysis (see ESI).

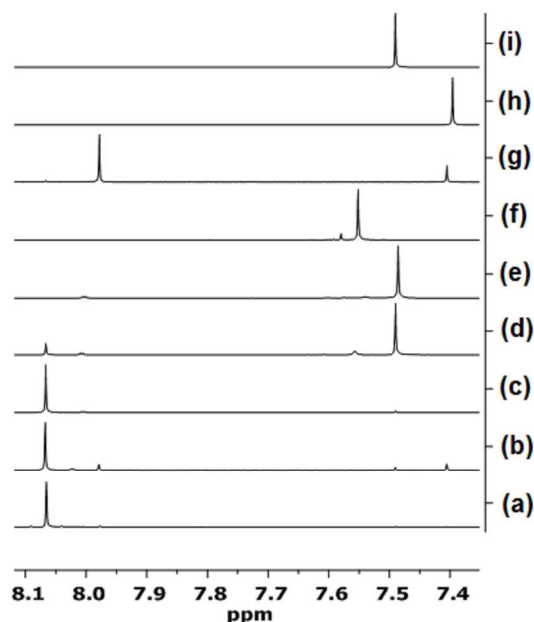


Figure 7. ¹H NMR spectroscopic analysis of the reaction of AuBr₂(*N*-TFS)(I'Pe) with AgOTf in acetone-*d*₆ over time. (a) AuBr₂(*N*-TFS)(I'Pe) only; (b) AuBr₂(*N*-TFS)(I'Pe), aged for 48 h; (c) AuBr₂(*N*-TFS)(I'Pe)/AgOTf (1:1), 10 mins; (d) as for (c), 4.5 h; (e) as for (c), 22.5 h; (f) AuBr(I'Pe)/AgOTf (1:1), 22.5 h; (g) solution of AuBr₃(I'Pe) only, aged for 48 h; (h) AuBr(I'Pe) only; (i) Au(*N*-TFS)(I'Pe) only.

A similar reaction of AuBr₂(*N*-TFS)(I'Pe) with Ag[Al(OC(CF₃)₃)₄] in acetone-*d*₆ afforded Au(*N*-TFS)(I'Pe) and a new broad signal at slightly higher chemical shift (δ 7.52) which we suggest is [Au(κ^1 -O=CMe₂)(I'Pe)]⁺[Al(OC(CF₃)₃)₄]⁻ (see ESI).

The binding of the AuBr₂(*N*-TFS)(I'Pe) and AgOTf toward 1-hexene in CD₂Cl₂ was evaluated to reveal evidence for any alkene-Au^{III} interaction (Table 4), in addition to showing whether liberated Br₂ could be sequestered by 1-hexene. For comparison, the reported spectroscopic data⁹ of [Au(μ_2 -H₂C=CHC₄H₉)(IPr)][SbF₆] is included in Table 4. A reduction in the alkene proton coupling constants, relative to free 1-hexene, is evidence for π -back donation, *i.e.* an increase in p character for the orbitals at carbon.

Table 4. Binding of 1-hexene to AuBr₂(*N*-TFS)(I'Pe) and AgOTf in CD₂Cl₂, as determined by ¹H NMR spectroscopic analysis (400 MHz).

Complex / Salt	1-Hexene (equiv.)	δ H ^a (ppm)	Coupling constant (Hz) ^b
-	-	5.82	17.0, 10.1, 6.7
AgOTf	2	6.21	17.7, 8.9, 6.6
[AuBr ₂ (<i>N</i> -TFS)(I'Pe)]	1	5.82	17.0, 10.1, 6.7
[AuBr ₂ (<i>N</i> -TFS)(I'Pe)] / AgOTf	1	6.26	18.0, 8.7, 6.5
[AuBr ₂ (<i>N</i> -TFS)(I'Pe)] / AgOTf	2	6.00	17.0, 10.1, 6.7
[Au(μ_2 -H ₂ C=CHC ₄ H ₉)(IPr)][SbF ₆]	1	6.05	17, 9, 4.5

^a The proton was observed as a *ddt*.

The ¹H NMR spectral data show no evidence for 1-hexene binding to neutral AuBr₂(*N*-TFS)(I'Pe), in the absence of AgOTf (Table 4). Upon mixing AuBr₂(*N*-TFS)(I'Pe) with 1 equiv. of AgOTf, the solution turns a cloudy colour (due to

AgBr formation). Addition of 1-hexene (1 equiv.) results in a shift of $\Delta\delta = 0.44$ ppm (relative to free 1-hexene). Coupling constants of 18.0 Hz ($\Delta J_{E-H} = +1$ Hz) for the *trans*-proton and 8.7 Hz ($\Delta J_{Z-H} = -1.4$ Hz) for the *cis*-coupling were recorded. Addition of 2 equiv. of 1-hexene leads to a reduction in the chemical shift ($\Delta\delta = 0.18$ ppm), with little change in coupling constants observed. The excess 1-hexene is therefore in exchange with the alkene-Au^{III} species or alkene-Ag^I species. After 24 h, the ¹H NMR spectrum had changed significantly, with a number of small ItPe imidazole signals corresponding to Au^I and Au^{III} species, in addition to a large broad signal (*ca.* 80% of the total imidazole proton signal) in the Au^I region. Another broad signal at δ 4.45-4.09 ppm was recorded, which we tentatively suggest is the alkene coordinated to Au^I; the broadness in the proton signal is due to fluxionality of the alkene as either Au(μ_2 -H₂C=CHC₄H₉)(*N*-TFS)(ItPe) or the naked cationic species [Au(μ_2 -H₂C=CHC₄H₉)(ItPe)]⁺. Signals corresponding to free 1-hexene and a new set of proton signals corresponding to 1,2-dibromohexane, *ca.* 50% abundance compared to free 1-hexene, *i.e.* 1 equivalent. After 24 h, there was no evidence of 1-hexene binding to Ag or Au. The ¹⁹F NMR spectrum showed a very large broad signal (-182.2 ppm) suggesting the observed alkene complex is that of Au(μ_2 -H₂C=CHC₄H₉)(*N*-TFS)(ItPe). In the absence of 1-hexene, the decomposition of AuBr₂(*N*-TFS)(ItPe) was not observed.

It is important to note that AgOTf alone binds to 1-hexene ($\Delta\delta = 0.39$ ppm; $\Delta J_{E-H} = +0.7$ Hz and $\Delta J_{Z-H} = -1.2$ Hz), which is similar to the binding of AuBr₂(*N*-TFS)(ItPe) / 1 equiv. AgOTf. Whilst AgBr is formed, we cannot rule out the involvement of chemical equilibria with AuBr₂(*N*-TFS)(ItPe) and AgOTf. Moreover, under the catalytic conditions there is an excess of substrate and solvent relative to the catalyst system, therefore solubilisation of all the metal species is possible.

(c) Mechanistic discussion

The experimental evidence from this study indicates that AuBr(I'Pe) is the most active catalyst for 1,5-enyne cycloisomerization in the series tested, showing first order behaviour. The Au^{III} catalyst, AuBr₃(I'Pe), mediates a slower reaction, which was successfully modelled kinetically as a second order process. The inclusion of a catalyst deactivation step was found necessary for the analysis. The ¹H NMR spectroscopic analysis revealed that AuBr₃(I'Pe) degrades to AuBr(I'Pe), even in the absence of AgOTf.

The presence of an *N*-imidate anion led to higher catalyst efficacy (defined as leading to full substrate conversion) in comparison with AuBr₃(I'Pe).¹⁰ Of the *N*-imidate series, AuBr₂(*N*-TFS)(I'Pe), is the most catalytically active. The nature of the NHC ligand exhibits a significant effect. For example, AuBr₂(*N*-phthal)(I'Pe) is twice as active as AuBr₂(*N*-phthal)(IMes).

Increasing the 1,5-enyne [9], and therefore the concentration of Au catalyst {AuBr₂(*N*-phthal)(I'Pe)}, leads to catalyst deactivation. Optimal catalyst performance was recorded at [9] between 0.1-0.2 M. At 0.5 M [9] it was necessary to model the kinetics to a second order process, again

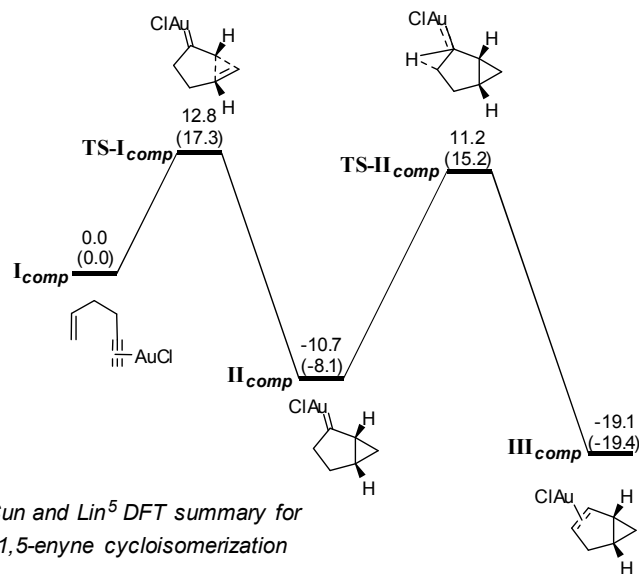
involving a catalyst deactivation step. Product inhibition is also possible at higher concentrations, and formation of Au colloids is visible by the naked eye (purple colouration, relating to the Au Plasmon band).

It was possible to assess subtle differences in catalyst behaviour by a concurrent cycloisomerization competition experiment, involving 1,5-enyne 9 and 1,6-enyne 11. The former gives 10 selectively, whereas 11 afford one of two products, 12a or 12b. Three catalysts were tested, namely AuBr(I'Pe), AuBr₂(*N*-TFS)(I'Pe) and AuBr₂(*N*-phthal)(I'Pe). In all cases, 1,5-enyne 9 was found to be more reactive than 1,6-enyne 11. Further analysis of the product ratios 12a:12b from the 1,6-enyne cycloisomerization reaction revealed key differences for the Au^{III} catalysts when compared to AuBr(I'Pe). After *ca.* 1.5 h, the ratios of 12a:12b for AuBr₂(*N*-TFS)(I'Pe) and AuBr₂(*N*-phthal)(I'Pe) mirrored the reaction mediated by AuBr(I'Pe). Therefore, while Au^{III} is still present, 12a is formed to a greater extent than in reactions solely mediated by Au^I.

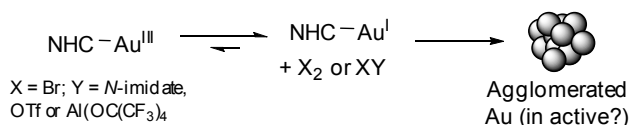
Our findings on the 1,5-enyne cycloisomerization process (9→11) are in-keeping with the DFT calculations reported by Sun and Lin.⁵ In that study, it was shown that the 1,5-enyne cycloisomerization reaction mediated by AuCl is both kinetically and thermodynamically favoured for the formation of the bicyclo[3.1.0]hexene product, with key catalytic steps (TS-I_{comp} carbene formation and TS-II_{comp} hydrogen migration) being of similar energy (Scheme 4).

From our experimental findings, we propose that Br₂ is liberated from cationic Au^{III}-NHC catalyst species, affording Au^I-NHC catalyst species *in situ*. The finding is supported by the liberation and trapping of the Br₂ by a sacrificial alkene (1-hexene) in the NMR spectroscopic investigations. Decomposition of the Au^I-NHC catalyst species affords Au colloids, which are most likely a moribund-form, especially as reduced catalyst performance is seen at higher [Au] and [9].

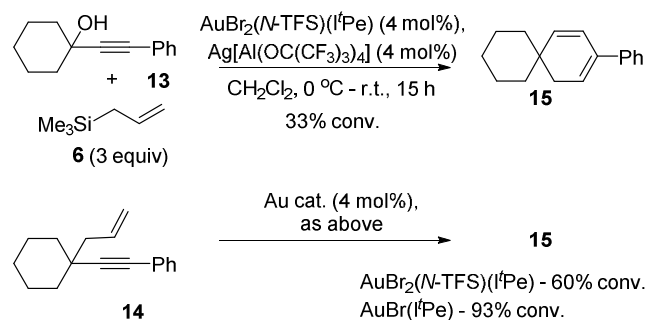
The binding experiments which explored the interaction of 1-hexene with AuBr₂(*N*-TFS)(I'Pe) / AgOTf, and AgOTf alone, demonstrates that 1-hexene binding is influenced in both cases. Crucially, 1-hexene mediates the decomposition of AuBr₂(*N*-TFS)(I'Pe) to Au(*N*-TFS)(I'Pe), which was not observed in the absence of 1-hexene in CD₂Cl₂. The results taken together demonstrate that unsaturated substrates are involved in: (i) catalyst activation to give Au^I, with concomitant decomposition of Au^{III}; (ii) solubilisation of the Ag salt, which is likely non-innocent in the catalysis. Subsequently, the nature of the coordinating ligand (and substrate and any impurities, as shown by substrate-aging experiments) is likely to affect catalytic turnover.



Scheme 4. Top: proposed mechanism for the 1,5-enyne cycloisomerization **9**→**10** (a role for Ag is not shown in the mechanism, although this cannot be ruled out). Bottom: DFT computed energies for the intermediates and transition states for the a 1,5-enyne cycloisomerization mediated by AuCl, reported by Sun and Lin.



Scheme 5. Catalyst activation and deactivation pathways.



Scheme 6. 1,5-enyne cycloisomerization leading to 1,3-cyclohexadiene formation.

Finally, it is important to emphasise that other products can result from the cycloisomerization of different 1,5-enynes, catalyzed by either AuBr(I'Pe) or AuBr₂(N-TFS)(I'Pe). In keeping with previous observations,^{3a,3d} we find that a 1,5-enyne containing a highly substituted carbon tether gives a cyclohexadiene product, both in the tandem nucleophilic substitution–1,5-enyne cycloisomerization (**13**→**14**→**15**) and the latter independent reaction (**14**→**15**) (Scheme 5). The outcome serves to highlight that the catalysts described here, and elsewhere, mirror related observations from other studies.

Conclusions

In this paper the ability of both Au^{III} and Au^I catalysts to mediate a 1,5-enyne cycloisomerization reaction has been examined. It was necessary to understand whether Au^{III} was being reduced under working catalyst conditions, especially as the success of the tandem nucleophilic substitution–1,5-enyne cycloisomerization relies on Au^{III} for the initial nucleophilic substitution step.^{6a}

The reaction kinetics for 1,5-enyne cycloisomerization, mediated by AuBr₂(N-imidate)(NHC) catalysts {where N-imidate = N-tetrafluorosuccinimide (N-TFS) or N-phthalimide (N-phthal) and NHC = N,N'-di-tert-pentylimidazol-2-ylidene (I'Pe)}, in the presence of AgOTf, revealed that the nature of the N-imidate anionic ligand influences catalyst efficacy. A direct comparison was made with Au^{III}Br₃(NHC), which exhibited significant catalyst deactivation in the absence of the stabilizing N-imidate ligand. In a concurrent cycloisomerization of 1,5- and 1,6-enynes (**9** and **11**) we were able to tease out subtle differences in the product distribution (**11**→**12a:12b**) during the early stages of catalytic turnover by the Au^{III} catalysts. NMR spectroscopic investigations have allowed the ease of reduction of AuBr₂(N-TFS)(NHC) to Au^IX(NHC) (where X = N-TFS or Br) to be examined. In these experiments, 1-hexene was shown to mediate Au^{III} decomposition. The liberation of Br₂ from the Au^{III} centre was trapped by this sacrificial alkene.

Taking together all of the results, we conclude, that under working catalyst conditions, cationic Au^{III} is reduced to Au^I. The role of Ag^I has been more difficult to understand (*i.e.* beyond simple bromide abstraction). The interplay of Au and Ag salts in 1,*n*-enyne cycloisomerization processes is currently being studied within our laboratories.

Experimental

General experimental details. All reactions involving silver salts were carried out in the absence of light. Deuterated and non-deuterated dichloromethane and acetonitrile were dried by passing through a column of activated alumina. Where necessary dichloromethane Infra-red spectra were recorded on a Unicam Research Series FT-IR spectrometer. Mass spectrometry was carried out using a Fisons Analytical (VG) Autospec instrument. ¹H and ¹³C NMR spectra were collected on a JEOL ECX400 spectrometer operating at 400 and 101 MHz, respectively, and referenced to residual solvent signals. ¹³C NMR signals are singlets unless otherwise stated. All column chromatography was performed using silica-gel (mesh 220-440) purchased from Fluka Chemicals with the solvent systems specified within the text. TLC analysis was performed using Merck 5554 aluminium backed silica plates, compounds were visualised using UV light (254 nm) and a basic aqueous solution of potassium permanganate. Melting points were measured in open capillary tubes using a Stuart SMP3 Digital Melting Point Apparatus and are uncorrected. 1-Phenyl-2-propyn-1-ol and AgOTf were purchased from Alfa Aesar. All

other chemicals were purchased from Sigma Aldrich Inc. and used without further purification unless otherwise stated. All of the Au catalysts used in this study have been reported; see our previous paper for full details.^{6b}

Kinetic Experiments

High resolution gas chromatographic (HRGC) analysis. GC was carried out on a Varian 430 instrument with a Factor Four Capillary column (VF-1ms, 15 m, 0.25 mm) and a flame ionisation detector. Samples of 10 μl were taken *via* syringe from the reaction mixtures at the specified time points. The samples were immediately quenched by addition of the aliquots to a solution of tetra-*n*-butylammonium chloride (8 mM, 20 μl) in CH_2Cl_2 . Conversion was determined *via* gas chromatography using a 1 μl sample injected directly into the instrument *via* syringe. Further sampling was carried out on selected aliquots over a period of time to ensure no further conversion occurred after quenching. The errors on the kinetic curves are recorded in the Tables detailed in the main text (see also Tables 1-3).

Values for the integrated areas of the GC signals corresponding to starting materials and products were inputted into Microsoft Excel spreadsheet software. This software was used to calculate percent conversions by comparison of starting material and product signal areas. The concentration of the species in solution was determined from the percent conversions and the initial starting material concentration. Selected aliquots were analysed by ^1H NMR spectroscopy to ensure consistency with conversions measured by GC.¹¹

Kinetic analysis. The reaction kinetics were calculated assuming a first order kinetic model by plotting $\ln[\text{enyne}]$ against time. Linear least-squares regression was used to calculate observed rate constants, initial rates and standard errors. The calculated concentrations of starting materials and products during the course of the reactions were also inputted into DynafitTM software (reported by Biokin). Nonlinear least-squares regression was used to fit the experimental kinetic data to predetermined molecular mechanisms as described in the main body of the paper. This was used to determine the order of reaction, observed rate constants, initial rates and standard errors and to fit curves to the kinetic data.

General procedure for the kinetic evaluation of the Au-catalysed cycloisomerization of 4-phenyl-1-hexen-5-yne (9) by gas chromatography

Au complex (3.2 μmol , 0.01 equiv.) and AgOTf (0.8 mg, 3.2 μmol , 0.01 equiv.) were mixed in CH_2Cl_2 (or DCE) in a screw cap vial (1 min) and the solvent removed *in vacuo*. A solution of 4-phenyl-1-hexen-5-yne (9) (50.0 mg, 321 μmol , 1 equiv.) in 1,2-dichloroethane (1.60 ml, 0.20 M) was added, the vial sealed with a rubber septum and a positive pressure of argon applied *via* an argon balloon. The mixture was stirred at 25 $^\circ\text{C}$ in the absence of light. Samples of 10 μl were taken *via* syringe and added immediately to a solution of tetra-*n*-butylammonium

chloride (8 mM, 20 μl) in CH_2Cl_2 . Conversion was determined *via* gas chromatography using a 1 μl sample. The chromatogram was run with an injector temperature of 250 $^\circ\text{C}$ and an initial oven temperature of 80 $^\circ\text{C}$ (0.5 mins), heated to 160 $^\circ\text{C}$, at a rate of 20 $^\circ\text{C}\cdot\text{min}^{-1}$, and maintained at 160 $^\circ\text{C}$ (1 minute). The retention times were: 2.58 mins for 4-phenyl-1-hexen-5-yne (9) and 3.89 mins for 3-phenylbicyclo[3.1.0]hex-2-ene (10).

General procedure for the kinetic evaluation of the Au-catalysed concurrent cycloisomerisation of 4-phenyl-1-hexen-5-yne (9) and dimethyl allylpropargylmalonate (11) by GC. Au complex (3.2 μmol , 0.01 equiv.) and AgOTf (0.8 mg, 3.2 μmol , 0.01 equiv.) were mixed in dichloromethane in a screw cap vial (1 min) and the solvent removed *in vacuo*. A solution of 4-phenyl-1-hexen-5-yne (9) (50.0 mg, 321 μmol , 1 equiv.) and dimethyl allylpropargylmalonate (11) (67.4 mg, 321 μmol , 1 equiv.) in 1,2-dichloroethane (1.60 ml, 0.20 M) was added, the vial sealed with a rubber septum and a positive pressure of argon applied *via* an argon balloon. The mixture was stirred at 25 $^\circ\text{C}$ in the absence of light. Samples of 10 μl were taken *via* syringe and added immediately to a solution of tetra-*n*-butylammonium chloride (8 mM, 20 μl) in CH_2Cl_2 (1 mL). Conversion was determined *via* gas chromatography using a 1 μl sample. The chromatogram was run with an injector temperature of 250 $^\circ\text{C}$ and an initial oven temperature of 80 $^\circ\text{C}$ (0.5 mins), heated to 160 $^\circ\text{C}$, at a rate of 10 $^\circ\text{C}\cdot\text{min}^{-1}$, and maintained at 160 $^\circ\text{C}$ (1 minute). The retention times were: 4.04 minutes for 4-phenyl-1-hexen-5-yne (9), 7.94 minutes for 3-phenylbicyclo[3.1.0]hex-2-ene (10), 5.53 minutes for dimethyl allylpropargylmalonate (11), 7.73 minutes for 12a and 8.15 minutes for 12b. The ^1H and ^{13}C NMR spectroscopic data for 9 and 10 (including representative NMR spectra) have been previously reported.⁶

[(1-Allylcyclohexyl)ethynyl]benzene (14). Prepared by a protocol based on that of Zhan and co-workers.¹² 1-Phenylethynyl cyclohexanol (13) (0.50 g, 2.5 mmol, 1 equiv.) and allyltrimethylsilane (6) (1.19 ml, 7.5 mmol, 3 equiv.) were mixed in acetonitrile (5 ml, dry) and FeCl_3 (anhydrous, 40 mg, 0.25 mmol, 0.1 equiv.) in acetonitrile (1 ml, dry) was added dropwise. The reaction was stirred at 60 $^\circ\text{C}$ for 18 h, reduced *in vacuo* and the product purified by column chromatography on silica gel, eluting with petroleum ether (40-60 $^\circ\text{C}$), to give the title compound as a colourless oil (0.249 g, 1.11 mmol, 44%). ^1H NMR (400 MHz, CDCl_3) δ 7.44-7.40 (m, 2H), 7.32-7.23 (m, 3H), 6.05 (ddt, J = 12.4, 9.3 and 7.5 Hz, 1H), 5.12 (m, 1H), 5.09 (m, 1H), 2.26 (dt, J = 7.2 and 1.3 Hz, 2H), 1.87-1.58 (m, 7H), 1.28-1.12 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 135.0, 131.6, 128.1, 127.4, 124.2, 117.1, 95.1, 83.3, 47.4, 37.6, 37.0, 26.1, 23.1. ESI+-MS m/z 301.1 (100%, $[\text{M}+\text{Ph}]^+$), 279.2 (11%), 245.1 (61%), 225.2 (68%, $[\text{MH}]^+$), 195.1 (20%), 167.1 (11%), 149.0 (23%), 126.0 (30%). ESI+-HRMS calcd. for $\text{C}_{17}\text{H}_{21}$ ($[\text{MH}]^+$) 225.1638; found 225.1633.

(4,4-Dimethylcyclohexa-1,5-dien-1-yl)benzene (15).

[AuBr(I'Pe)] (3.6 mg, 7.4 μmol , 0.02 equiv.), Ag[Al(OC(CF₃)₃)₄] (76) (8.0 mg, 7.4 μmol , 0.02 equiv.) and [(1-allylcyclohexyl)ethynyl]benzene (14) (78.3 mg, 0.350 mmol, 1 equiv.) were dissolved in dichloromethane (2 mL) and stirred (0 °C - r.t., 15 h). The reaction mixture was reduced *in vacuo* and purified by column chromatography on silica gel, eluting with petroleum ether (40-60 °C), to give the title compound as a colourless oil (64.8 mg, 0.289 mmol, 83%; 93% conversion noted by NMR). ¹H NMR (400 MHz, CDCl₃) δ 7.46-7.43 (m, 2H, aromatic CH), 7.39-7.34 (m, 2H, aromatic CH), 7.31-7.26 (m, 1H, aromatic CH), 6.30 (dd, $J = 9.9$ and 1.8 Hz, 1H, alkene CH d), 6.05 (app. t, $J = 4.8$ Hz, 1H, alkene CH c), 5.97 (d, $J = 9.9$ Hz, 1H, alkene CH e), 2.36 (d, $J = 4.8$ Hz, 2H, CH₂ b), 1.64-1.39 (m, 10H, cyclohexyl CH₂). ¹³C NMR (100 MHz, CDCl₃) δ 140.3 (C), 137.8 (2 peaks, alkene CH e), 134.9 (C), 128.3 (CH), 126.8 (CH), 125.3 (CH), 123.4 (alkene CH d), 122.0 (alkene CH c), 36.3 (broad, cyclohexyl CH₂), 36.2 (alkene CH₂ b), 33.4 (cyclohexyl C), 26.3 (cyclohexyl CH₂), 21.8 (cyclohexyl CH₂). EI+-MS m/z 224 (100%, [M]⁺), 181 (7%), 167 (34%), 153 (8%), 142 (7%), 115 (6%), 91 (6%), 49 (34%).

NMR Experiments.

Generation of Au^{III} cationic species from AuBr₂(N-TFS)(I'Pe) and AgOTf. In acetone-*d*₆: AuBr₂(N-TFS)(I'Pe) (10 mg, 1.36x10⁻⁵ mols) was reacted with AgOTf (3.5 mg, 1.36x10⁻⁵ mols) in acetone-*d*₆ (0.67 mL) at 25 °C. The mixture was stirred for 1 h and then a ¹H NMR spectrum was recorded (500 MHz). Characterisation details are included in the main body of the text.

In CD₂Cl₂/CD₃CN: AuBr₂(N-TFS)(I'Pe) (5 mg, 6.8x10⁻⁶ mols) was reacted with AgOTf (7 mg, 6.8x10⁻⁶) or Ag[Al(OC(CF₃)₃)₄] (7.3 mg, 6.8x10⁻⁶ mols) in CD₂Cl₂ (0.6 mL) and CD₃CN (0.2 mL) at 25 °C. The mixture was stirred for 1 h and then a ¹H NMR spectrum was recorded (500 MHz). Characterisation details are included in the main body of the text.

Binding of 1-hexene to AuBr₂(N-TFS)(I'Pe) and AgOTf, and AgOTf alone. AuBr₂(N-TFS)(I'Pe) (10 mg, 1.36x10⁻⁵ mols) was reacted with AgOTf (3.5 mg, 1.36x10⁻⁵ mols) in CD₂Cl₂ (0.6 mL) for 1 h. Then, 1-hexene (3.4 μL , 2 equiv.) was added and then NMR spectra were recorded (500 MHz). In separate experiments the equivalents of 1-hexene were varied. Characterisation details are included in the main body of the text (Table 4 gives further details). The interaction of AgOTf with 1-hexene was examined on the same scale as above, without the Au^{III} complex. See ESI for NMR spectral data.

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Notes and references

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- (a) A. Arcadi, *Chem. Rev.*, 2008, **108**, 3266-3325. (b) Z. Li, C. Brouwer and C. He, *Chem. Rev.*, 2008, **108**, 3239-3265. (c) Zigang Li, Chad Brouwer and Chuan He, *Chem. Rev.*, 2008, **108**, 3351-3378. (d) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Commun.*, 2007, 333-346.
- (a) Y. Harrak, C. Blaszykowski, M. Bernard, K. Cariou, E. Mainetti, V. Mouriès, A. Dhimane, L. Fensterbank and M. Malacria, *J. Am. Chem. Soc.*, 2004, **126**, 8656-8657. (b) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.*, 2004, **126**, 10858-10859. (c) Horino, Y.; Yamamoto, T.; Ueda, K.; Kuroda, S.; Toste, F. D. *J. Am. Chem. Soc.*, 2009, **131**, 2809-2811. (d) Toullec, P. Y.; Michelet, V. *Top. Curr. Chem.*, 2011, **302**, 31-80.
- (a) J. Sun, M. P. Conley, L. Zhang and S. A. Kozmin, *J. Am. Chem. Soc.*, 2006, **128**, 9705-9710. (b) L. Zhang and S. A. Kozmin, *J. Am. Chem. Soc.*, 2004, **126**, 11806-11807. (c) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.*, 2004, **126**, 8654-8655. (d) Gagosz, F. *Org. Lett.*, 2005, **7**, 4129-4132.
- (a) N. Marion, G. Lemièrre, A. Correa, C. Costabile, R. Ramón, X. Moreau, P. D. Frémont, R. Dahmane, A. Hours, A. Lesage, J. C. Tablet, J. P. Goddard, V. Gandon, L. Cavallo, L. Fensterbank, M. Malacria, S. P. Nolan, *Chem. Eur. J.*, 2009, **15**, 3243-3260. (b) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Rev.*, 2008, **108**, 3326-3350. (c) T. Godet and P. Belmont, *Synlett*, 2008, 2513-2517. (d) S. M. Ma, S. C. Yu and Z. H. Gu, *Angew. Chem., Int. Ed.*, 2006, **45**, 200-203. (e) L. Zhang, J. Sun and S. A. Kozmin, *Adv. Synth. Catal.*, 2006, **348**, 2271-2296. (f) C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2004, **43**, 2402-2406.
- T. Fan, X. Chen, J. Sun and Z. Lin, *Organometallics*, 2012, **31**, 4221-4227
- (a) J. P. Reeds, A. C. Whitwood, M. P. Healy and I. J. S. Fairlamb, *Organometallics*, 2013, **32**, 3108-3120. (b) J. P. Reeds, A. C.

- Whitwood, M. P. Healy and I. J. S. Fairlamb, *Chem. Commun.*, 2010, **46**, 2046-2049.
- 7 Dynafit program published by Biokin, see: P. Kuzmic, *Anal. Biochem.*, 1996, **237**, 260-273.
- 8 (a) Gaillard, S.; Slawin, A. M. Z.; Bonura, A. T.; Stevens, E. D.; Nolan S. P. *Organometallics*, 2010, **29**, 394-402. (b) A. S. K. Hashmi, M. C. Blanco, D. Fischer and J. W. Bats, *Eur. J. Org. Chem.*, 2006, 1387-1389. (b) N. Morita and N. Krause, *Eur. J. Org. Chem.*, 2006, 4634-4641. (c) S. Komiya and J. K. Kochi, *J. Am. Chem. Soc.*, 1976, **98**, 7599-7607. (d) S. Komiya, T. A. Albright, R. Hoffmann and J. K. Kochi, *J. Am. Chem. Soc.*, 1976, **98**, 7255-7265.
- 9 T. J. Brown, M. G. Dickens and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2009, **131**, 6350-6351.
- 10 We have seen *N*-imidate ligand effects in catalytic cross-coupling chemistry, see: (a) J. L. Serrano, L. García, J. Pérez, E. Pérez, J. García, G. Sánchez, P. E. Sehnal, S. De Ornellas, T. J. Williams and I. J. S. Fairlamb, *Organometallics*, 2011, **30**, 5095-5109. (b) I. J. S. Fairlamb, P. Sehnal and R. J. K. Taylor, *Synthesis*, 2009, 508-510. (c) M. J. Burns, I. J. S. Fairlamb, A. R. Kapdi, P. Sehnal and R. J. K. Taylor, *Org. Lett.*, 2007, **9**, 5397-5400. (d) C. M. Crawforth, I. J. S. Fairlamb, A. R. Kapdi, J. L. Serrano, R. J. K. Taylor and G. Sanchez, *Adv. Synth. Catal.*, 2006, **348**, 405-412. (e) S. Burling, C. M. Crawforth, I. J. S. Fairlamb, A. R. Kapdi, R. J. K. Taylor and A. C. Whitwood, *Tetrahedron*, 2005, **61**, 9736-9751. (f) C. M. Crawforth, I. J. S. Fairlamb and R. J. K. Taylor, *Tetrahedron Lett.*, 2004, **45**, 461-465. (g) I. J. S. Fairlamb, A. R. Kapdi, A. F. Lee, G. Sánchez, G. López, J. L. Serrano, L. García, J. Pérez and E. Pérez, *Dalton Trans.*, 2004, 3970-3981. (h) J. L. Serrano, I. J. S. Fairlamb, G. Sanchez, L. Garcia, J. Perez, J. Vives, G. Lopez, C. M. Crawforth, R. J. K. Taylor, *Eur. J. Inorg. Chem.*, 2004, 2706-2715. (i) I. J. S. Fairlamb, A. R. Kapdi, J. M. Lynam, R. J. K. Taylor and A. C. Whitwood, *Tetrahedron* **2004**, *60*, 5711-5718. (j) C. M. Crawforth, S. Burling, I. J. S. Fairlamb, R. J. K. Taylor and A. C. Whitwood, *Chem. Commun.*, 2003, 2194-2195.
- 11 E. H. Niemelä, A. F. Lee and I. J. S. Fairlamb, *Tetrahedron Lett.* 2004, **45**, 3593-3595.
- 12 Zhan, Z.; Yu, J.; Liu, H.; Cui, Y.; Yang, R.; Yang, W.; Li, J. *J. Org. Chem.* **2006**, *71*, 8298-8301.