Gold-catalysed room-temperature cycloisomerisation of alkynes and unactivated enolisable ketones†

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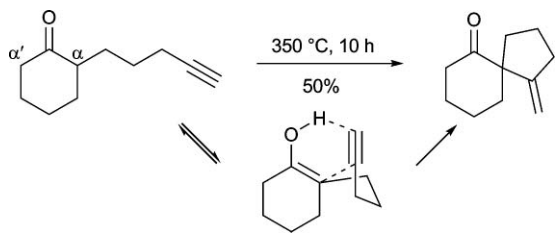
The cycloisomerisation of simple keto-alkynes proceeds at room temperature under the mild conditions of gold catalysis. Bicyclic fused and spiro compounds can be obtained by overall 5-*exo* and 6-*exo* carbon–carbon bond-forming cyclisations.

Transformations which lead to increased molecular complexity from simple, readily-introduced, functionality are inherently appealing. One such process is the Conia-ene cyclisation in which a carbon–carbon bond is formed by α-modification of an enolisable carbonyl group with an alkyne (Scheme 1). This thermal vapour- or liquid-phase pericyclic reaction proceeds with complete retention of substrate constitution.[1,2] However, applications of this transformation are limited by the high temperatures required.

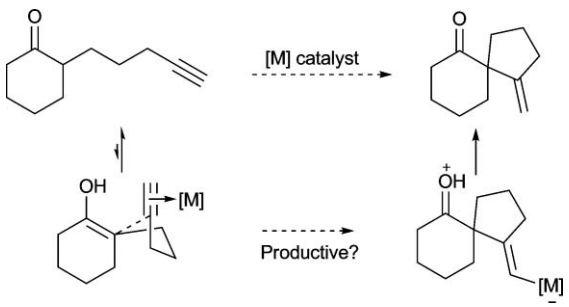


Scheme 1 The thermal Conia cyclisation.

The use of alkyne activation has proven a highly successful strategy for the cyclisation of related substrates where *C*-nucleophilicity of the carbonyl compound is enhanced through structural alteration, for example as β-ketoesters, or silyl enol ethers.[2–7] In particular, widely applicable and efficacious carbon–carbon bond forming processes have been reported using these strategies alongside gold-catalysed alkyne activation.[7,8]

In general, π-acid activation of alkynes for reaction with well-defined nucleophiles is highly efficient.[9] For reactions of keto-alkynes, the addition of a carbonyl oxygen to a metal-activated alkyne has been established to trigger a range of transformations.[10] Exceptions to this reaction mode have recently been reported. π-Acid alkyne activation has been coupled with aminocatalysis for *in situ* activation of a carbonyl unit to form *C*-nucleophilic enamine intermediates and favour a carbocyclisation.[11,12] Additionally, a few examples of α′-carbonyl substitution have been observed through 6-*endo*-dig cyclisation onto aryl-capped alkynes at elevated temperatures.[13]

We had wondered if the high reaction temperatures and/or activation of the carbonyl moiety were always necessary to achieve this powerful type of transformation: Would π-acid activation of an alkyne be sufficient for direct carbon–carbon bond formation with the *C*-nucleophilic enol tautomer of an unactivated enolisable carbonyl unit? If such activation were productive even when the nucleophile is in low effective concentration, a direct 'Conia-like' *exo*-mode carbocyclisation of keto-alkynes might be achievable under mild reaction conditions (Scheme 2). This would avoid the synthetic impact associated with separately (pre)activating the carbonyl compound. In this paper we report that the overall transformation is possible.



Scheme 2 Proposed keto-alkyne cyclisation.

Our study focused on the use of cyclic ketones with a tethered terminal alkyne to access fused carbocycles. Initial trials were performed using keto-alkyne **1a**, readily obtained by conjugate addition of malonate to cyclohexenone. Catalyst screening appeared promising; simple gold and platinum metal salts did yield the desired cyclic product **2a** or its isomer **3a**, albeit only in low conversion, even at elevated temperatures (see Supporting Information†). The use of the cationic gold species $Ph_3PAuNTf_2$[14] afforded the conjugated enone cycloisomerisation product **2a** with reasonable conversion and yield even at room temperature (Table 1, entry 1). Variations on these reaction conditions were explored, including choice of solvent (Table 1, entries 1–5), counterion (Table 1, entries 6–10)[15] and gold source (Table 1, entries 11 and 12). Exomethylene isomer **3a** was not observed in more than trace amounts. Control reactions show the gold to be a necessary part of the reaction system (Table 1, entries 13–16). In the absence of Ph_3PAuCl, AgOTf afforded only very low conversion. The use of triflic and *p*-toluene sulfonic Brønsted acids gave rapid decomposition and no reaction respectively. A 10 : 1 dichloromethane–water solvent mixture employed in the gold-catalysed cyclisation of silyl enol ethers[7a] gave no conversion in this reaction (Table 1, entry 5).

Ultimately, substrate **1a** was converted cleanly into bicyclic enone **2a** with only a reasonable loading of gold catalyst at room temperature by 5-*exo* cyclisation [Ph_3PAuCl/AgOTf (6 mol%),

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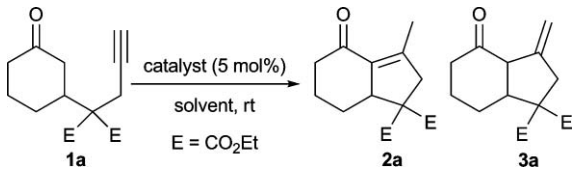
† Electronic supplementary information (ESI) available: Experimental details and analytical data for new compounds. See DOI: 10.1039/c003473h

Table 1 Survey of reaction conditions[a]



Entry	Catalyst[b]	Solvent	Time/h	Yield (%) **2a**(**1a**)[c]
1	$Ph_3PAuNTf_2$	CH_2Cl_2	19	59(3)
2	$Ph_3PAuNTf_2$	Toluene	19	16(27)
3	$Ph_3PAuNTf_2$	THF	19	22(60
4	$Ph_3PAuNTf_2$	$ClCH_2CH_2Cl$	19	66(20)
5	$Ph_3PAuNTf_2$	CH_2Cl_2–H_2O[d]	19	0(79)
6	Ph_3PAuBF_4	CH_2Cl_2	24	26(18)
7	$Ph_3PAuNTf_2$	CH_2Cl_2	3.5	43(44)
8	$Ph_3PAuOTf$	CH_2Cl_2	3.5	77(12)
9	$Ph_3PAuSbF_6$	CH_2Cl_2	3.5	46(3)
10	Ph_3PAuPF_6	CH_2Cl_2	3.5	0(92)
11	$(Ph_3PAu)_3OBF_4$	CH_2Cl_2	2.5	0(100)
12	$Dppm(AuCl)_2$/AgOTf[e]	CH_2Cl_2	19	9(84)
13	AgOTf	CH_2Cl_2	3.5	<5(59)
14	HOTf	CH_2Cl_2	0.25	0(0)[f]
15	HOTf[g]	CH_2Cl_2	1	0(0)[f]
16	*p*TSA	CH_2Cl_2	2.5	0(95)

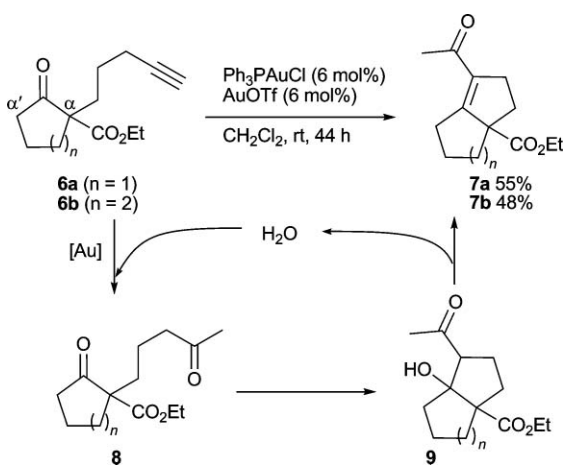
[a] A solution of **1a** (0.2 mmol) in solvent (0.1 M) was added to a mixture of the (pre)catalyst. [b] With the exception of commercially available $Ph_3PAuNTf_2$, Ph_3PAuX catalysts were prepared *in situ* by mixing equimolar quantities of Ph_3PAuCl and the required Ag(I) salts. [c] Yields determined by ^1H NMR against a known quantity of 1,2,4,5-tetramethylbenzene. [d] In a 10 : 1 ratio. [e] 10 mol% AgOTf employed. [f] Complete degradation was observed. [g] 0.5 mol% loading.

CH_2Cl_2 (0.1 M)]. As the yield from the gold-catalysed room-temperature cyclisation of **1a** was comparable to the reactions of analogous substrates containing preformed enolates, we prepared a range of cyclic ketones with tethered alkynes to study the process. The precursor keto-alkynes **1a–i** and **4a–b** were readily assembled by conjugate addition to an enone, or α-alkylation respectively, and then subjected to the gold catalysis. Successful *exo*-mode cycloisomerisations of the keto-alkynes were observed allowing a range of bicyclic fused and spiro carbon frameworks to be prepared from simple precursors (Table 2). The process could be used in 5 or 6-membered ring formation.

The size of the existing ring in the starting material does play an important role in the cyclisation. Substrates containing 5, 6 and 7-membered rings afforded the desired products in good yields (Entries 1–6). In most cases the conjugated alkene is formed as the sole or major isomer. However, 8-membered ring substrate **1g** only cyclised slowly to give the exomethylene product **3g** as the major isomer, albeit in low yield. Cyclisation of **1e** led to a mixture of alkene isomers**2e**.

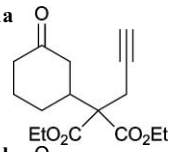
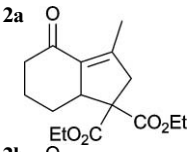
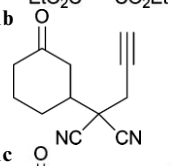
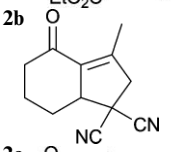
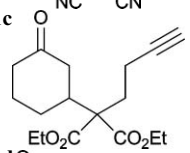
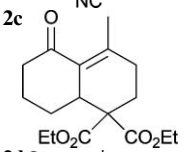
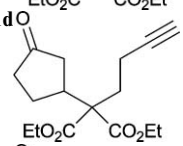
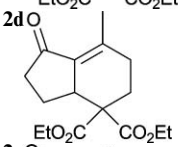
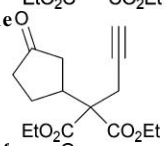
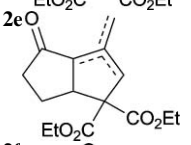
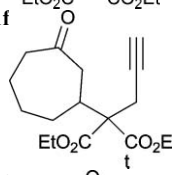
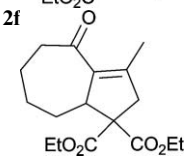
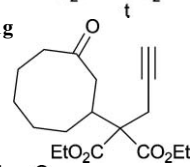
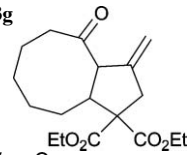
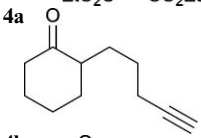
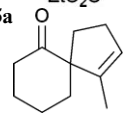
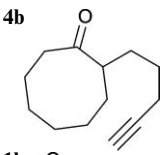
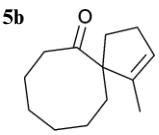
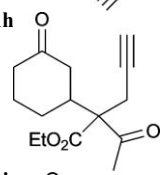
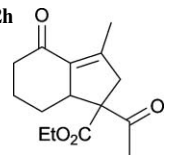
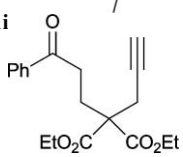
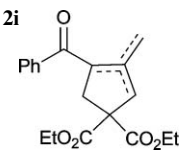
Spirocyclic compounds could also be accessed *via* this methodology (Table 2, entries 8 and 9), and also show that the presence of malonate or equivalent unit in the tether is not necessary. The room temperature cyclisation of substrate **4a** serves as a useful comparison to the thermal Conia-cyclisation (Scheme 1). Under gold catalysis at room temperature, internal alkene product **5a** was isolated in 61% yield (Table 2, Entry 8). Under thermal conditions, a temperature of 350 °C led to the exomethylene cyclisation product in 50% yield (Scheme 1).[1] In contrast, we found that thermal cyclisation of **1a** also led to the conjugated enone isomer **2a**.[16] Substrates **4a**, **4b** and **1h** are of particular interest as α-elaboration of the carbonyl compound occurs even though the carbonyl oxygen could act as a nucleophile to the activated alkyne.[10] Substrate **1h**, which bears two enolisable carbonyl groups and hence the potential for several alternative routes, led to the bicyclic product **2h** in moderate yield (Table 1, Entry 10). Cycloisomerisation of an acyclic keto-alkyne precursor **1i** was also viable, although the product was isolated as a mixture of three isomers **2i** in a 10 : 3 : 1 ratio with the major being α,β-unsaturated enone.

Substrates **6a** and **6b** with non-enolisable α-positions were then explored under the reaction conditions (Scheme 3). Bicyclic enones **7** were formed slowly. These products are inconsistent with either reaction of the alkyne at the enolisable α′-position or direct enone formation through oxetenium intermediates.[13,17] Instead,



Scheme 3 Formation of bicyclic enones.

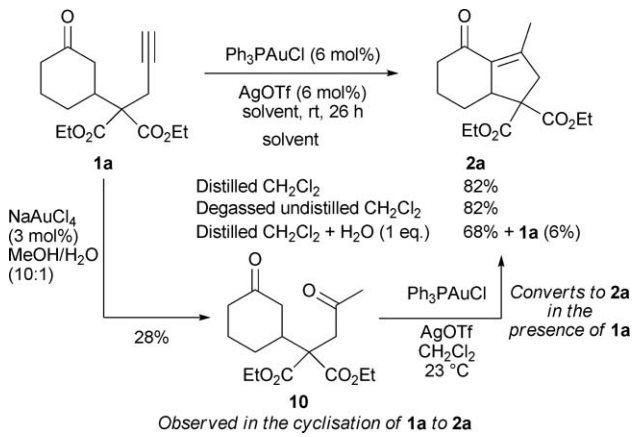
Table 2 Gold-catalysed cyclisation of keto-alkynes[a]

Entry	Substrate	Product	Time/h	Yield (%)[b]
1	**1a** 	**2a** 	24	87
2	**1b** 	**2b** 	34	81
3	**1c** 	**2c** 	22	61[c]
4	**1d** 	**2d** 	17	79[d]
5	**1e** 	**2e** 	24	98[e]
6	**1f** 	**2f** 	24	64
7	**1g** 	**3g** 	48	26[f]
8	**4a** 	**5a** 	18	61
9	**4b** 	**5b** 	16	58
10[g]	**1h** 	**2h** 	15	44
11[h]	**1i** 	**2i** 	24	51[i]

[a] Reactions were carried out using Ph_3PAuCl (6 mol%), AgOTf (6 mol%) in CH_2Cl_2 (0.1 M) at RT, for 0.4 mmol of **1a**. [b] Isolated yield after flash chromatography. [c] + 7% isomeric products. [d] + 2% isomeric products. [e] Three enone isomers in a ratio of 3.7 : 2 : 1 (α,β-unsaturated : exomethylene β,γ-unsaturated : β,γ-unsaturated). [f] Small amounts of unidentified products were also recovered alongside 16% of **1g**. [g] 1 : 1.2 ratio of diastereomers [h] Using 10 mol% catalyst loading. [i] Three enone isomers in a 10 : 3 : 1 ratio (α,β-unsaturated : exomethylene β,γ-unsaturated : β,γ-unsaturated). See Supporting Information.†

formation of **7** can be explained by a gold-promoted hydration of the alkyne in the presence of adventitious water to afford diketones **8**.[18] Using **6b** a small quantity of **8b** was isolated from the reaction mixture. Subsequently, intramolecular aldol dehydration with preferential formation of a five-membered ring would afford the observed product and regenerate water. The latter step may be promoted by the gold catalyst or traces of Brønsted acid generated *in situ* from it.[13,19]

In light of this result, we considered the possibility that a similar hydration–aldol dehydration pathway could account for all the cyclisations rather than direct carbon–carbon bond-formation. Subjecting keto-alkyne **1a** to the hydrative conditions developed by Liu [$PtCl_2$, CO (1 atm), dioxane–H_2O, 100 °C, 2.5 h] afforded complete conversion with the cyclic enone **2a** formed in 66% NMR yield alongside several byproducts at 6 mol% catalyst loading.[20,21,22] As previously seen in our study, larger quantities of water shut down the gold-catalysed reaction completely (Table 1, entry 5). Similarly, when 1 equivalent of water was added to the reaction mixture, the reaction progress was significantly retarded, and a lower overall combined yield of product and recovered starting material was obtained (Scheme 4).



Scheme 4 Study of the possible hydration–aldol-dehydration process. Yields determined by ^{1}H NMR against a known quantity of 1,2,4,5-tetramethylbenzene.

However, the use of degassed yet undistilled CH_2Cl_2 gave the same yield of **2a** as did using distilled CH_2Cl_2.[23] When using dry solvent the hygroscopic silver salts employed in these reactions are a potential source of adventitious water. No product was observed when the reaction was run in the presence of activated molecular sieves to counter this issue. These results confirm that a small amount of water is necessary for the cyclisation of **1a**. However, larger proportions of water have a negative effect which is apparently due to catalyst deactivation and increasing levels of either product or starting material degradation.

To further explore the role of water, the immediate product of alkyne hydration, diketone **10**, was independently prepared. Unoptimised $NaAuCl_4$-promoted hydration gave **10** in moderate yields alongside a mixture of **1a** and **2a**. No reaction was observed when **10** was subjected to the standard gold-catalysed cyclisation conditions. However, when a small amount of **1a** was added to a solution of Ph_3PAuCl–AgOTf and **10** in CH_2Cl_2 after 2 h, a reaction was initiated and product **2a** was formed. On near complete consumption of **10**, analysis of the product mixture confirms that both keto-alkyne **1a** and diketone **10** are converted into enone **2a** under the reaction conditions (See Supporting Information†). The formation of a small amount of **10** was observed when the gold-catalysed cyclisation of **1a** was performed in an NMR tube and monitored regularly by ^{1}H NMR (See Supporting Information). Addition of independently synthesised **10** to this reaction confirmed this observation. On depletion of the keto-alkyne, remaining diketone was also consumed. These results prove that, despite the low levels of water, intermolecular alkyne hydration occurs under the reaction conditions. Furthermore, a species generated in the reaction of **1a** is capable of mediating aldol dehydration of **10**. While the direct carbon–carbon bond forming process (Scheme 2) can not be eliminated as a possibility, as water would also aid the required keto–enol tautomerisation, the alkyne-hydration aldol-dehydration pathway is shown to be at least competitive with this intramolecular cyclisation.

In summary, we have demonstrated the overall cycloisomerisation of unactivated ketones with alkynes at room temperature under gold catalysis. This straightforward process has been used to assemble a range of fused and spiro carbocyclic structures from simple precursors under mild conditions. The role of water is finely poised between being an integral component of the reaction system and contributing to catalyst and substrate degradation. Further investigations into the precise role of water in these reactions are under way alongside a wider study of gold-catalysed reactions of keto-alkynes. These results will be reported in due course.

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Notes and references

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