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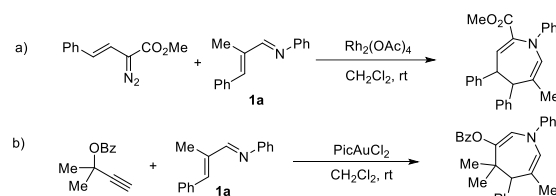
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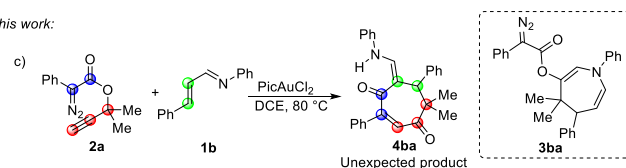
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Conjugated cycloheptene-1,4-dione-enamines are cycloaddition products from a surprising rearrangement in a Au(III)-catalysed reaction between propargyl aryldiazoacetates and cinnamyl imines. This complex transformation occurs through an initial rapid Au(III)-catalysed [4+3]-cycloaddition to form dihydroazepinyl aryldiazoacetates followed by a subsequent uncatalyzed domino transformation that occurs by sequential [3+2]-cycloaddition/nitrogen extrusion and acyloxy migration/retro-Michael addition/tautomerization.

[4+3]-Cycloaddition is one of a relatively few synthetic methods available to form seven-membered rings.¹ Combining a four-atom π -system with a three-atom π -system, this methodology produces carbocyclic and heterocyclic compounds, many of which are of biological interest.² Allyl or oxyallyl cations have been used as three-atom π -systems with dienes as the four-atom π -system in symmetry-allowed processes.³ Recently, however, catalytic [4+3]-cycloaddition reactions of vinylimines to form dihydroazepines with either the metal vinylcarbenes from styryldiazoacetates⁴ or gold vinylcarbenes from propargyl benzoate esters⁵ have been reported (Scheme 1a and 1b). In these stepwise reactions azepine derivatives are formed selectively and in high yields. In the former case the metal carbene from the styryldiazoacetate combines with the vinylimine to form an azomethine ylide that undergoes electrocyclic ring closure. In the latter case gold(III) catalysis transforms the propargyl benzoate to a gold vinylcarbene that also combines with a vinylimine to form an azepine product. Recent results from our laboratory have demonstrated that gold catalysis in reactions with propargyl diazoacetates involves selective acyloxy migration initiated with



This work:



Scheme 1. Metal-catalysed reactions of unsaturated imines with vinyl carbene precursors.

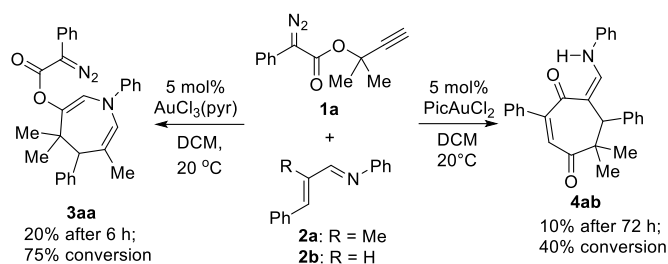
the carbon-carbon triple bond and leaves the diazo functionality intact.⁶ We thought that by simple modification of propargylbenzoate to propargyl phenyldiazoacetate **2a** we could form a dihydroazepinyl phenyldiazoacetate **3ba** which could be directed to undergo subsequent catalytic metal carbene transformations.⁷ Instead, we have discovered a new and unexpected formal cycloaddition/rearrangement that dramatically reorganizes the reactant atoms, including conversion of the reactant ester to a diketone **4ba** (Scheme 1c).

Treatment of propargyl phenyldiazoacetate **2a** at room temperature in the presence of 5.0 mol% PicAuCl₂ with α,α -methyl-*trans*-cinnamyl *N*-phenylimine **1a**, which was reported to be the optimal imine substrate for [4+3]-cycloaddition reactions with α,α -dimethylpropargyl benzoate,⁴ resulted in a complex product mixture. This process occurred with complete loss of propargyl phenyldiazoacetate **2a** within 30 minutes without observable formation of **3aa**, but with reduction of the Au(III) catalyst to metallic gold. The use of alternative Au(I) catalysts, including AuCl, Au(JohnPhos)SbF₆, and Au(Ipr)BF₄ that are commonly used in transformations of propargyl esters,⁷ also failed to give the anticipated [4+3]-cycloaddition product. With the use of 5.0 mol% AuCl₃(pyr) **3aa** was formed in a mixture of products after a 6 h reaction time at room temperature, but in

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Scheme 2. Surprising outcome in gold(III)-catalyzed reactions between propargyl diazoacetates and cinnamyl imines.

only 20% yield (See supporting information, Table S1). However, replacing **1a** with cinnamylimine **1b**, which was previously reported to undergo cycloaddition in very low yield,⁸ gave a new compound after 72 h that was isolated in 10% isolated yield. This product did not have the diazo functional group, or an anticipated ester functionality, and was highly colored (**4ab**, Scheme 2). To optimize formation of this product, various gold catalysts and reaction conditions were investigated (See supporting information, Table S2), but the highest yield of this compound was obtained from the reaction performed at 80 °C in 1,2-dichloroethane (DCE) for 6 h in the presence of 5.0 mol% PicAuCl₂. The limiting factor in these reactions was reduction of PicAuCl₂ to metallic gold that occurred at 80 °C in separate reactions with propargyl phenyldiazoacetate **2a** and cinnamyl *N*-phenylimine **1b**, but did not occur with α -methyl-*trans*-cinnamyl *N*-phenylimine **1a** or with either propargyl benzoate or propargyl phenylacetate under the same conditions.

Attempts to determine the structure of this new compound spectroscopically gave partial connectivities, demonstrated the loss of dinitrogen, and pointed to the conversion of the ester to ketones, but its final confirmation awaited X-ray determination. Various derivatives were prepared, but only with **4ha** from the reaction between propargyl phenyldiazoacetate **2a** and cinnamyl *N*-1-naphthylimine **1h** was a compound suitable for single crystal analysis obtained. X-ray diffraction revealed a structure in which the carbon atoms of the original propargyl phenyldiazoacetate were significantly rearranged, that the ester was converted to a diketone, and whose structure depicted a keto-enamine with an intramolecular hydrogen bond between nitrogen and an adjacent carbonyl group of a 1,4-enedione (Figure 1). Extrusion of dinitrogen from propargyl phenyldiazoacetate **2a** occurred, and the carbon atoms of the

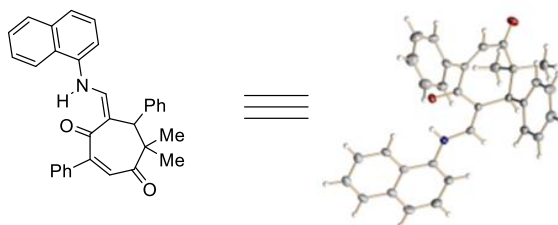
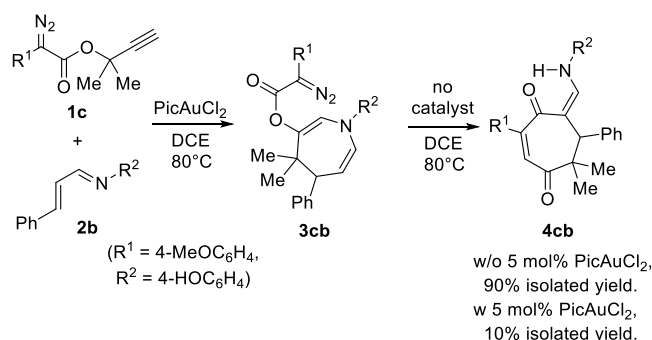


Figure 1. X-Ray structure of **4ha**. The CCDC 1509853 contains supplementary crystallographic data for **4ha**.

seven-membered ring came from three parts of the combined reactants.

This extraordinary structural rearrangement obviously occurred after the combination of the imine reactant with an intermediate formed by the gold catalysed reaction with the propargyl phenyldiazoacetate. We were confident that gold catalysis occurred with the acetylenic functional group rather than with the diazo group, but was this rearrangement the result of a transformation from the gold-catalysed [4+3]-cycloaddition product? To address this question propargyl phenyldiazoacetate **2a** was reacted with cinnamyl *N*-phenylimine **1b** at the lower reaction temperature of refluxing CDCl₃ in the presence of 5 mol% PicAuCl₂. The [4+3]-cycloaddition product **3ba** could be observed as a reaction intermediate within 5 min, and complete conversion to **4ba** occurred within 12 h (Figure S1). The separation and isolation of the pure [4+3]-cycloaddition product was limiting, but after an extensive survey **3cb** could be isolated in 36% isolated yield from **1c** and **2b** by quenching the reaction after 5 min at 80 °C in DCE. This compound was stable at room temperature but when heated in DCE at 80 °C for 1 h in the absence of catalyst, cycloheptene-1,4-dione enamine **4cb** was obtained in 90% isolated yield. In contrast, when the [4+3]-cycloaddition product **3cb** was treated with 5.0 mol% PicAuCl₂ in DCE at 80 °C, complete decomposition of **3cb** occurred within 1 h and resulted in a complex product mixture from which only 10% of **4cb** was obtained (Scheme 3).



Scheme 3. Control experiments for the formation of **4cb** from **3cb**.

Under thermal reaction conditions isolated **3cb** underwent an elaborate process to form cycloaddition product **4cb**. The progress of the reaction, monitored by HPLC, exhibited first order dependence on the concentration of **3cb** and provided a first order rate constant $k_{\text{obs}} = 3.6 \times 10^{-4} \text{ sec}^{-1}$ at 61 °C in DCE. Further examination of this reaction over temperatures ranging from 61 °C to 75 °C provided rate constants from which its activation parameters were calculated (see supporting information): $E_{\text{act}} = 22.6 \text{ kcal/mol}$, $\Delta H^{\ddagger}_{298} = 22.0 \text{ kcal/mol}$ and $\Delta S^{\ddagger}_{298} = -9.21 \text{ cal/(mol} \cdot \text{ } ^\circ\text{C)}$. These activation parameters are consistent with an intramolecular process that we assume to be initiated by dipolar cycloaddition of the diazo ester.⁹

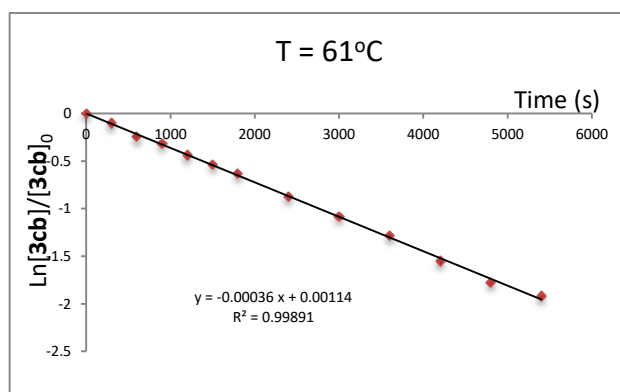
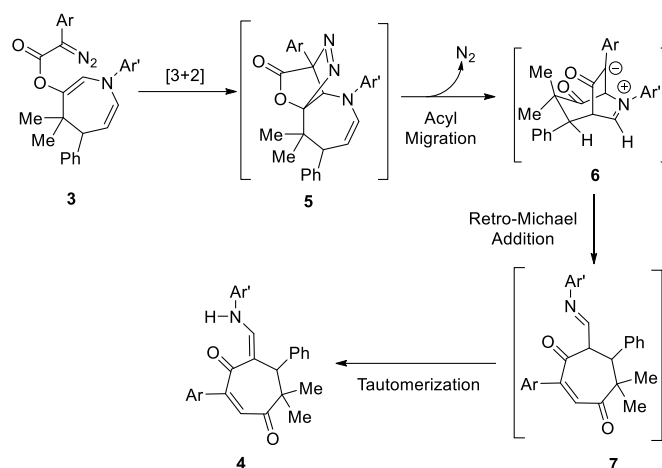


Figure 2. Linear relationship between reaction time and $\ln[3cb]/[3cb]_0$. Reaction performed in DCE at 61°C.

The vinyl gold carbene intermediates generated by 1,2-acyloxy migration¹¹ of the propargyl aryldiazoesters undergo formal [4+3]-cycloaddition with unsaturated imines **1** to afford dihydroazepines **3**.⁵ These products are derivative of those reported by Toste and Shapiro and are reasonably formed by the same reaction pathway. The previously preferred use of imine **1a** is consistent with its relative inability to reduce the gold(III) catalyst compared to **1b**, and this reduction prepares the reaction system for the metal-free conversion of dihydroazepinyl aryldiazoacetates **3** to 1,4-cycloheptenedione-enamine **4** that is not prevented by gold-catalysed dinitrogen extrusion from **3**. We speculate that this unique process occurs through a four-step sequential [3+2]-cycloaddition/dinitrogen extrusion and acyloxy migration/retro-Michael addition/tautomerization cascade pathway, which is shown in Scheme 4. The [3+2]-cycloaddition of diazo compounds with alkenes that forms pyrazolines **5** is a well-known process, which has been reported to occur intermolecularly¹¹ and intramolecularly.¹² The newly formed pyrazolines **5** are highly strained, which causes them to spontaneously undergo a dinitrogen extrusion/acyloxy migration cascade process to afford azomethine ylides **6** that continues the cascade via a retro-Michael addition¹³ and tautomerization¹⁴ to complete the process forming 1,4-cycloheptenedione-enamine **4**. Attempts to detect reaction intermediates along this pathway were unsuccessful.

Although 1,4-enedione¹⁵ and ketoenamine¹⁶ functionalities are common in nature, the extended conjugation seen in structure **4** is uncommon. The prevalence of 1,4-enediones in bioactive natural products and medicinal compounds is well established.¹⁷ Ketoenamine structures are common in medicinal and biochemistry, chemosensors, and energy storage.¹⁸ However, the combined 1,4-enedione-ketoenamine structural arrangement is rare but has been identified in muscicapines **8** (Figure 3),¹⁹ a recently discovered class of sesquiterpene alkaloids found in the roots of a shrub native to Northeastern Brazil (*Croton muscicapa*).

In efforts to determine the generality of the gold-catalysed cycloaddition and subsequent rearrangement, structural modifications on both the propargyl aryldiazoacetates and the cinnamyl arylimines were investigated under the optimized reaction conditions.⁹ Product yields obtained in these reactions



Scheme 4. Proposed mechanism for the dihydroazepine phenyldiazoacetate cascade rearrangement.

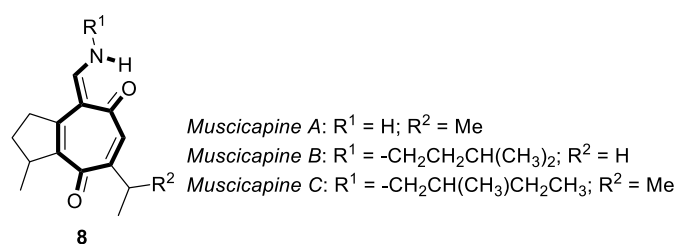
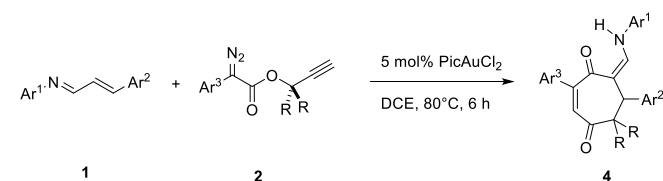


Figure 3. Structure of muscicapines **8**.

are those of the pure materials obtained after column chromatography. Propargylic aryldiazoacetates **2** with either electron-donating or electron-withdrawing groups at the *para* position underwent the gold-catalysed transformation smoothly in 6 h with moderate to high yields (Table 1, entries 1-4). *Ortho* substituted propargylic aryldiazoacetates (**2f** and **2g**) gave reasonable yields of **4bf** and **4bg** (Table 1, entries 5 and 6). Unsaturated imines **1c-1g** with arylimine-derived *para* substituents Ar¹ – including ethers, phenols, and halides – underwent this cycloaddition-rearrangement under the stated reaction conditions (Table 1, entries 7-11). Sterically hindered 1-naphthylamine-derived **1h** also formed the 1,4-enedione-ketoenamine product (**4ha**) in 68% yield (Table 1, entry 12 and Figure 1). Imine **1i** with a bulky *N*-mesityl group gave **4ia** highest yield of any of the substrates that were employed (Table 1, entry 13). That *p*-nitrocinnamylaldehyde-derived and *p*-methoxycinnamylaldehyde-derived unsaturated imines **1j** and **1k** gave the corresponding products **4ja** and **4ka** in comparable yields shows the electronic tolerance of the reactant *trans*-cinnamyl-*N*-phenylimines (Table 1, entries 14 and 15). Using cyclopentylpropargyl phenyldiazoacetate, which was easily obtained from 1-ethynylcyclopentanol, the rearranged product **4bg** was formed in basically the same yield as its dimethyl analog **4ba** (Table 1, entry 16). Maximum UV/Vis absorptions for these compounds (305 and 413 nm) show little variation with aryl substitutions (± 7 nm), but their molar absorptivities are generally greater than 10,000 M⁻¹cm⁻¹.

Table 1. The scope of gold-catalysed reactions of propargyl aryldiazoacetates **2** with unsaturated imines **1**.^[a]

Entry	1	Ar ² /Ar ³	2	Ar ¹ /R	4	Yield of 4 (%) ^[b]
1	1c	4-HOC ₆ H ₄ /Ph	2b	4-	4cb	68
2	1b	Ph/Ph	2c	MeOC ₆ H ₄ /Me	4bc	65
3	1b	Ph/Ph	2d	4-BrC ₆ H ₄ /Me	4bd	55
4	1b	Ph/Ph	2e	4-O ₂ NC ₆ H ₄ /Me	4be	43
5	1b	Ph/Ph	2f	2-BrC ₆ H ₄ /Me	4bf	52
6	1b	Ph/Ph	2g	2-O ₂ NC ₆ H ₄ /Me	4bg	55
7	1c	4-HOC ₆ H ₄ /Ph	2a	Ph/Me	4ca	64
8	1d	4-MeOC ₆ H ₄ /Ph	2a	Ph/Me	4da	65
9	1e	4-BrC ₆ H ₄ /Ph	2a	Ph/Me	4ea	61
10	1f	4-ClC ₆ H ₄ /Ph	2a	Ph/Me	4fa	60
11	1g	4-FC ₆ H ₄ /Ph	2a	Ph/Me	4ga	56
12	1h	2-Naphhyl/Ph	2a	Ph/Me	4ha	68
13	1i	2,4,6-Me ₃ C ₆ H ₂ /Ph	2a	Ph/Me	4ia	70
14	1j	Ph/4-MeOC ₆ H ₄	2a	Ph/Me	4ja	67
15	1k	Ph/4-O ₂ NC ₆ H ₄	2a	Ph/Me	4ka	59
16	1b	Ph/Ph	2g	Ph/-(CH ₂) ₄ -	4bg	65

[a] Reactions were performed on 0.20 mmol scale: a solution of **2** (0.24 mmol) in 2.0 mL solvent was added to a solution of **1** (0.20 mmol) and 5.0 mol% of PicAuCl₂ in 2.0 mL of DCE under a nitrogen atmosphere at 20 °C, and the resulting reaction mixture was stirred at 80 °C for 6 h. [b] Yields are isolated yields after chromatography.

In conclusion, we have developed a general and efficient method for the synthesis of conjugated 1,4-cycloheptenedione-enamines **4** from easily prepared materials. This synthesis results from a [4+3]-cycloaddition between the gold-carbene formed from propargyl aryldiazoacetates catalysed by PicAuCl₂, followed by an unprecedented cascade process that occurs without metal catalysis through a sequential [3+2]-cycloaddition/dinitrogen extrusion and acyloxy migration/retro-Michael addition/tautomerization to produce **4** in moderate overall yields. The success of this synthesis is based on rapid catalytic [4+3]-cycloaddition and both coordination of PicAuCl₂ with the cinnamylimine and reduction of PicAuCl₂ by the diazo compounds and cinnamylimines to allow uncatalysed formation of **4**. Reaction conditions are balanced to effect [4+3]-cycloaddition without reduction of PicAuCl₂, but then allow the domino transformation of the [4+3]-cycloaddition product (**3**) to occur without interference by PicAuCl₂ that causes the destruction of **3**.

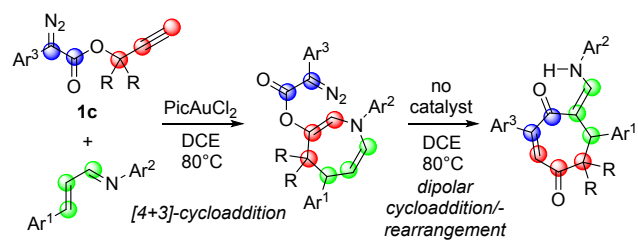
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Conflicts of interest

There are no conflicts to declare.

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Surprising rearrangement of dihydroazepinyl aryldiazoacetates from a gold-catalysed [4+3]-cycloaddition to conjugated cycloheptene-1,4-dione-enamines.