Regioselectivities in alkyne activation: synthesis of 2-(bicyclo[3.1.0]hexan-1-yl)furan derivatives by Au-catalyzed cyclization and cyclopropanation†

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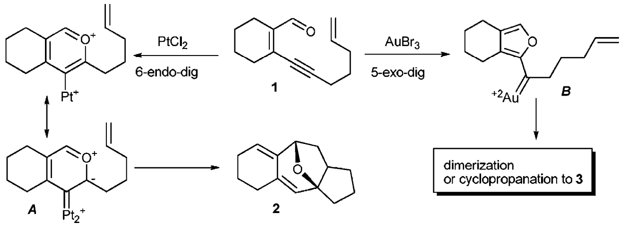
Received (in Cambridge, UK) 15th July 2008, Accepted 29th August 2008
First published as an Advance Article on the web 1st October 2008
DOI: 10.1039/b812077c

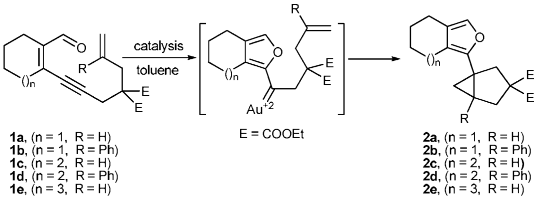
2-Alkynyl-1-cycloalkenecarbaldehydes, in the presence of gold catalysts, undergo aurative cyclization *via* the 5-*exo-dig* mode to form Au-carbene intermediates which react with a double bond to form the corresponding cyclopropanes.

With alkynophilic metal cations such as Au^{3+}, *ortho*-alkynylbenzaldehydes are known to form metal-pyrylium species which undergo cycloaddition with an unsaturated bond.[1] Recently, we reported the [3 + 2] cycloaddition of Rh- and Au-pyrylium species, derived from *ortho*-alkynylbenzaldehydes, with an unsaturated bond.[2,3] The Yamamoto group also reported a gold-catalyzed benzannulation involving intramolecular [4 + 2] cycloaddition of Au-pyrylium species with dienophiles.[4] More recently, we have paid our attention to Pt-pyrylium species, derived from 2-alkynyl-1-cycloalkenecarbaldehydes, since those might serve structurally diverse polycyclic skeletons for syntheses of complex molecules.[5] The platinum cation is also alkynophilic and is prone to form Pt-pyrylium complexes. Combining properties associated with platinum cations, we could report their powerful catalytic activities toward 2-alkynyl-1-cycloalkenecarbaldehydes **1** to form reactive pyrylium intermediates ***A*** which would undergo cycloaddition *via* a [3 + 2] route and subsequent γ-deprotonation–protodemetalation to afford [*m*,7,*n*]-tricycles **2** having an oxygen bridge (Scheme 1). Herein we wish to report a unique behavior of gold cations compared to platinum cations, that enynals **1** in the presence of gold cation would undergo aurative cyclization *via* the 5-*exo-dig* mode to form the intermediate ***B*** which would react with the unsaturated bond intramolecularly.[6]



Scheme 1 Two possible paths of a metal carbene complex.

Table 1 Intramolecular cyclopropanation of enynals with Au



Entry	Substrate	5 mol% catalyst	Temperature/°C, time/h	Product (% yield)
1	**1a**	$AuBr_3$	25, 0.1	**2a** (10)
2	**1a**	AuCl	0, 1	**2a** (10)
3	**1a**	$AuCl(PPh_3)$	60, 12	**2a** (35)
4	**1b**	$AuBr_3$	25, 16	**2b** (37)
5	**1c**	$AuBr_3$	25, 0.5	**2c** (40)
6	**1d**	$AuBr_3$	25, 0.5	**2d** (55)
7	**1e**	$AuBr_3$	25, 0.5	**2e** (45)

We chose the substrate **1a** as well as its analogs **1b–1e** for exploring the modes of reaction with Au catalysts, since **1a** has shown somewhat suspicious reactivity in our previous study.[7] We used three gold compounds as catalysts. Preliminary results on Au-catalyzed reactions of substrates **1a–1e** showed that cyclopropanations were competitive along with dimerizations depending on the ring size of the cycloalkenes (Table 1). Cyclization of **1a** with $AuBr_3$, AuCl, and $AuCl(PPh_3)$ afforded a dimeric but uncharacterizable product as a major product along with the cyclopropanation product **2a** in low yields (entries 1–3). The 2-alkynyl-1-cycloheptenecarbaldehyde **1c** and 2-alkynyl-1-cyclooctenecarbaldehyde **1e** exhibited better cyclopropane formation: **2c** and **2e** were obtained in 40% and 45% yields, respectively.

The introduction of a phenyl substituent at the internal position of the olefin was tolerated, as evident from the moderate conversion of **1b** and **1d** into **2b** and **2d** with complete regioselectivities (Table 1, entries 4 and 6), suggesting that the 5-*exo*-cyclization might be favored with gold catalysts.[8] Next, nitrogen-containing substrates (**1f–1k**, Fig. 1) were studied for this transformation. The cyclizations were carried out with 5 mol% of $AuBr_3$ in toluene at rt. All six substrates smoothly underwent the present reaction to afford the corresponding products **2f–2k**, respectively.

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† Electronic supplementary information (ESI) available: Experimental procedures and spectral data of products **2a–2t**, **3m**, and **4m**. See DOI: 10.1039/b812077c

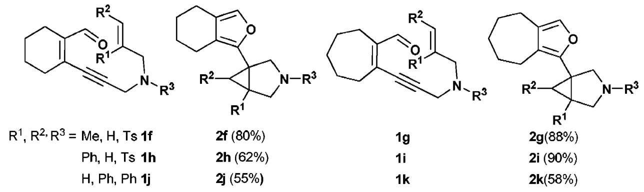


Fig. 1 Au-catalyzed cyclization of nitrogen-containing substrates.

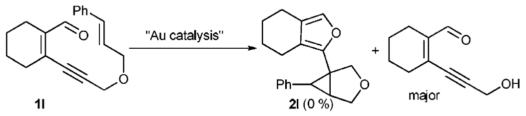


Fig. 2 Attempted Au-catalyzed cyclization of an oxygen-containing substrate.

Then, we tested an oxygen-containing substrate **1l** (Fig. 2). Unfortunately under our conditions substrate **1l** was not cyclized into the corresponding product **2l**, and the hydrolyzed product was isolated as a major product.

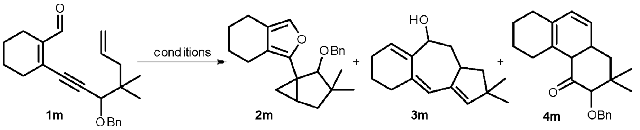
To extend this transformation to more diverse substrates, we prepared enynal (**1m**) and surveyed various catalytic conditions including Pt catalysts as summarized in Table 2.

The use of gold tribromide in either toluene or 1,4-dioxane led to **2m** exclusively at ambient temperature in good to excellent yields (entries 1–2). Gold chloride in toluene was also a good catalyst for this purpose (entry 3). It is worthwhile to note that the platinum compounds catalyzed cyclizations but afforded a mixture of **2m**, **3m**, and **4m**.[9] We have examined some other substrates having a benzyloxy group at the propargylic position (**1m–1r**) and TBS-protected substrates **1s** and **1t** (Fig. 3).

Fortunately, all substrates exhibited the same mode of reaction under $AuBr_3$ catalysis: furanylation and cyclopropanation (**2m–2t**).[10] As the ring size increased from six to seven, the reactions proceeded more smoothly.

The most plausible reaction pathway for the intramolecular cycloaddition of **1m** is illustrated in Scheme 2. Initially, the alkynophilic metal cation would activate the triple bond to enhance the electrophilicity. In the case of gold, the subsequent pathway **a**, 5-*exo-dig* nucleophilic attack of the oxygen on a Au–alkyne complex, would form the (2-furyl)-carbenoid intermediate ***B***.[11] And cyclopropanation, a characteristic reaction of carbenoids with a double bond, would occur to afford **2m**. Platinum compounds, however, might undergo both 5-*endo-dig* and 6-*endo-dig* pathways, to give **2m** in low yield along with **3m** and **4m** in moderate yields. Platinum-pyrylium intermediate ***C*** with a pendant double bond undergoes two different modes of cyclization: [3 + 2] cycloaddition to ***D*** followed by γ-deprotonation–protodemetalation to afford [6,7,5]-tricycle **3m**. Formation of **4m** can be understood *via* the intramolecular [4 + 2] cycloaddition of ***C*** followed by base-promoted fragmentation.

Table 2 Optimization of the reaction conditions for the Au/Pt-catalyzed reaction of enynal **1m**



Entry	5 mol% catalyst	Solvent	Temperature/°C, time/h	Product (% yield)
1	$AuBr_3$	Toluene	rt, 0.25	**2m** (80)
2	$AuBr_3$	Dioxane	rt, 0.25	**2m** (75)
3	AuCl	Toluene	rt, 0.5	**2m** (72)
4	$PtCl_2(PPh_3)_2$	Toluene	110, 5	**3m** (42), **4m** (48)
5	$PtCl_2$	Toluene	100, 1.5	**3m** (18), **4m** (30)
6	$PtCl_4$	Toluene	110, 1	**2m** (17), **3m** (20), **4m** (50)

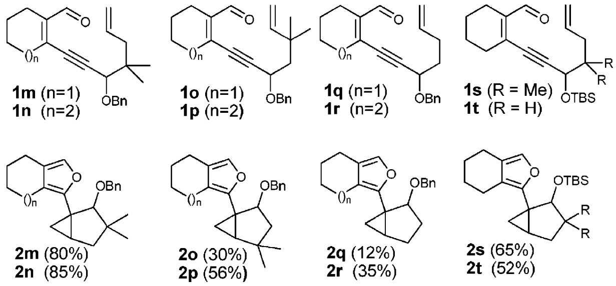
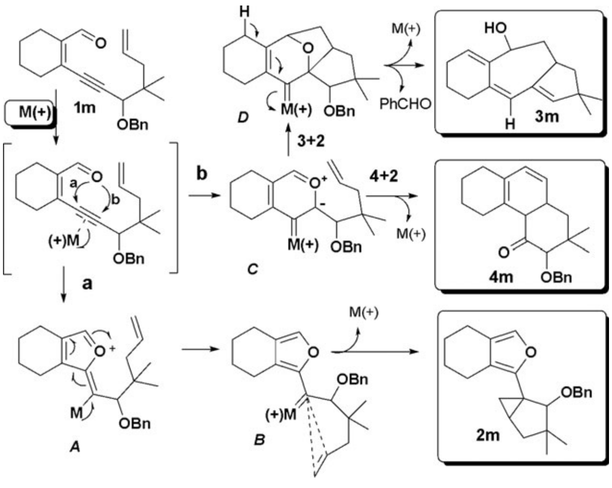


Fig. 3 Au-catalyzed cyclization of carbon-containing substrates.



Scheme 2 Mechanistic hypothesis for the metal-catalyzed cyclization of **1m**. [M] = Au or Pt complex.

In conclusion, we have shown a novel Au-catalyzed transformation of 2-alkynyl-1-cycloalkenecarbaldehydes into furanyl-substituted cycloalkyl-fused cyclopropanes in good yields.

Financial support was provided by a grant from the Korea Research Foundation (KRF-2007-314-C00164) and BK21.

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