

Gold-Catalyzed Intermolecular Formal (3+2) Cycloaddition of Stabilized Vinylidazo Derivatives and Electronically Unbiased Allenes

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The reaction of electronically unbiased allenes with alkenyldiazo compounds in the presence of gold catalysts provided alkylidenecyclopentene derivatives resulting from a formal intermolecular (3+2) carbocyclization. A stepwise mechanism involving initial activation of the diazo component and subsequent formation of an allyl cation intermediate has been proposed. This process represents the first intermolecular gold-catalyzed cycloaddition involving non-activated allenes.

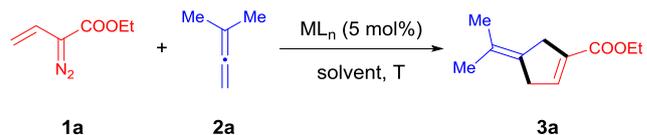
Allene derivatives have fascinated and stimulated chemists for decades. In particular, in the last twenty years transition metal-mediated/catalyzed transformations of allenes have flourished becoming valuable synthetic tools in organic chemistry.¹ Very recently, gold complexes have also emerged as very active catalysts in transformations involving allenes enabling researchers to discover new and useful reactions.² Although the mechanistic course of these transformations is still far from being fully elucidated,³ it is generally accepted that the coordination of the allene to gold generates an electrophilic species, which would evolve to the final products through diverse mechanistic pathways. Specifically, a number of gold-catalyzed cycloadditions of allene derivatives have been recently reported. Whereas most of these cycloaddition reactions rely on either intramolecular processes⁴ or the use of activated allenes (very often allenamides),⁵ the intermolecular cycloaddition reactions of unbiased allene derivatives remain challenging.⁶

On the other hand, transition metal-catalyzed transformations of stabilized vinylidazo derivatives have received in the last two decades great attention. The recent introduction of gold-complexes as catalysts in these transformations has paved the

way for the search of new mechanistic pathways expanding the synthetic relevance of these already useful diazo derivatives.⁷ In this regard, continuing with our interest in the search for new synthetic applications based on gold-catalyzed transformations of stabilized vinylidazo compounds, herein we report the gold-catalyzed formal (3+2) cycloaddition toward electronically unbiased allenes. To the best of our knowledge, this (3+2) cycloaddition reaction represents not only the first gold-catalyzed intermolecular cycloaddition involving non activated allenes but also a very unusual reactivity pattern in allene chemistry.

On the outset, we studied the reaction of ethyl 2-diazobut-3-enoate (**1a**) and an excess (4 equiv) of 3-methylbuta-1,2-diene (**2a**) in the presence of a series of transition metal catalysts (5 mol%) in dichloromethane as solvent at room temperature (Table 1, see the ESI for full details on the screening study).

Table 1. Catalyst screening



entry	ML _n	solvent	T (°C)	Yield of 3a (%) ^a
1	AgSbF ₆	CH ₂ Cl ₂	rt	17
2	AuCl ₃	CH ₂ Cl ₂	rt	<5
3	AuCl	CH ₂ Cl ₂	rt	<5
5	(Ph ₃ P)AuNTf ₂	CH ₂ Cl ₂	rt	<5
6	(JohnPhos)AuNTf ₂	CH ₂ Cl ₂	rt	49
7	(IPr)AuNTf ₂	CH ₂ Cl ₂	rt	36
8	[IPrAu(MeCN)][SbF₆]	CH₂Cl₂	rt	75
9	[IPrAu(MeCN)][SbF ₆]	DCE	50	23
10	[IPrAu(MeCN)][SbF ₆]	DMF	rt	5

^a Isolated yields

Unfortunately, rhodium and copper complexes, which are arguably the most useful catalysts in transformations involving vinylidazo compounds, did not afford any coupling product but mixtures of products resulting from the decomposition of the starting vinylidazo compound **1a**. Interestingly, AgSbF₆

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provided the cyclopentene derivative **3a** arising from a formal (3+2) cyclization, although in unsatisfactory yield (17%, entry 1). Next, by screening a variety of gold complexes (entries 2-8), [Au(IPr)(CH₃CN)]SbF₆ was identified as the most efficient catalyst, providing cycloadduct **3a** in 75% yield after chromatographic purification (entry 8). Significantly, under these reaction conditions neither dimers of the starting diazocompound⁸ nor regioisomers of **3a** were detected in the reaction mixture. Heating the reaction in DCE (entry 9) did not improve the yield of **3a**. On the other hand, changing the solvent from dichloromethane to DMF completely shut down the reaction (entry 10).

With suitable cyclization conditions in hand, we then focused on whether this gold-catalyzed carbo-(3+2) cyclization process could be extended to other 1,1-disubstituted allene derivatives **2** and vinyldiazo compounds **1** (Table 2).

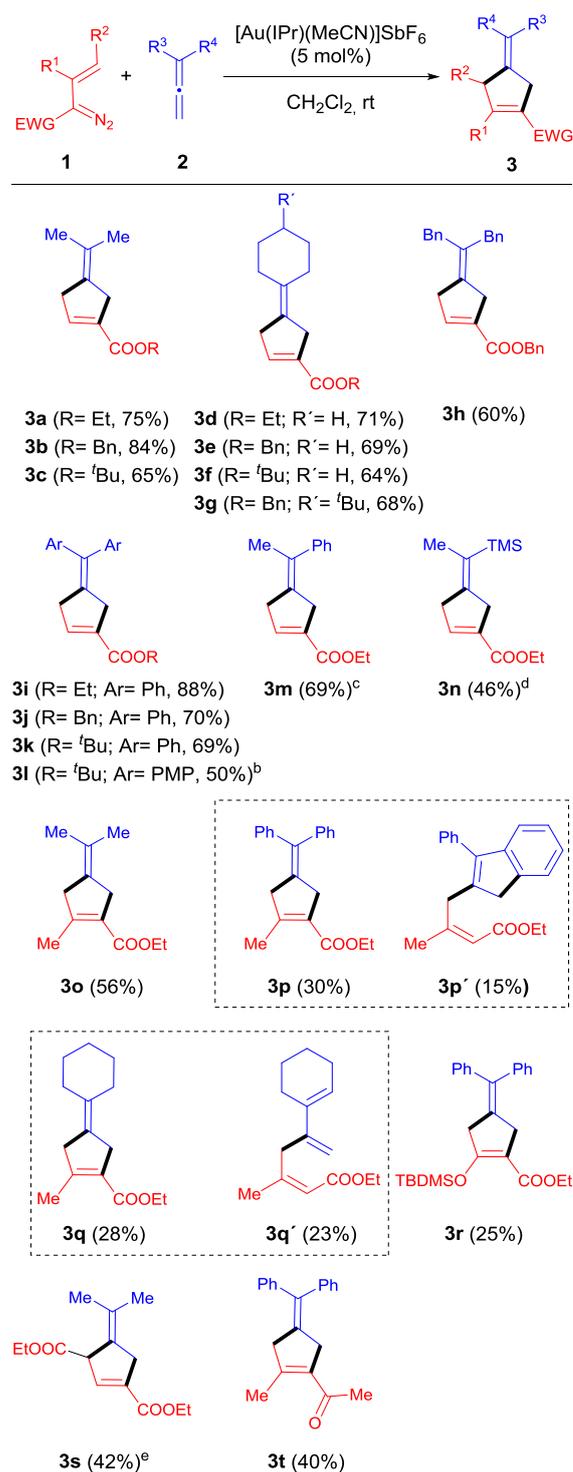
First, we found that the nature of the ester substituent has little impact on the outcome of the reaction with 3-methylbuta-1,2-diene (**2a**). Thus, benzyl substituted vinyldiazo compound (**1b**; R¹ = R² = H, EWG = COOBn) undergoes the cyclization process affording the corresponding cycloadduct **3b** in comparable yield. Likewise, the use of *tert*-butyl 2-diazo-but-3-enoate (**1c**; R¹ = R² = H, EWG = COO^tBu) delivered the expected cyclopentene derivative **3c** in moderate yield.

Regarding the allene coupling partner, the process was found to tolerate a wide range of substitution. Thus, vinylidenecyclohexane (**2b**) and 1-(*tert*-butyl)-4-vinylidenecyclohexane (**2c**) give rise to the cyclopentene derivatives **3d-g** in reasonable yields. Benzyl groups on the allene (allene **2d**, R³ = R⁴ = Bn) were also tolerated affording the corresponding (3+2) adduct **3h** in moderate yield. 1,1-Diarylsubstituted allene derivatives (**2e**, R³ = R⁴ = Ph; **2f**, R³ = R⁴ = 4-methoxyphenyl) also reacted successfully under the conditions described above to give cycloadducts **3i-l**. On the other hand, the reaction of **1a** with 3-phenylbuta-1,2-diene (**2g**) afforded the expected (3+2) cycloadduct **3m** in good yield and selectivity (69%, *Z/E* = 15:1). Likewise, 3-trimethylsilylbuta-1,2-diene (**2h**) furnished cyclopentene derivative **3n** in moderate yield and selectivity.

The use of vinyldiazo compounds substituted at the vinyl moiety was next explored. Under the standard conditions, vinyldiazo compounds with an alkyl group at the C β atom (vinyldiazoacetate **1d**; R¹ = Me, R² = H, EWG = COOEt) also led to the corresponding cycloadducts **3o-q**, albeit in modest yields. Enol diazoacetates, useful diazo derivatives in metal-catalyzed transformations, also participated in this gold-catalyzed cycloaddition although with a significant decrease in the yield. Indeed, reaction of enol diazoacetate **1e** (R¹ = OSi^tBuMe₂, R² = H, EWG = COOEt) with 1,1-diphenylallene (**2e**) delivered the corresponding cycloadduct **3r**. An ester function at the C γ position was also tolerated (diazoacetate **1f**; R¹ = H, R² = EWG = COOEt), as exemplified by the formation of **3s** (42%).

Finally, this new gold-catalyzed reaction could also be applied to diazo derivatives with other stabilizing groups. Thus, treatment of diazoketone **1g** (R¹ = Me, R² = H, EWG = COMe) with 1,1-diphenylallene (**2e**) furnished **3t** in moderate yield.

Table 2. Gold(I)-catalyzed formal (3+2) cycloaddition of stabilized vinyldiazo compounds **1** and 1,1-disubstituted allenes **2**^a

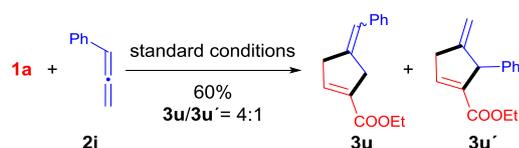


^a Yield of isolated products after column chromatography. ^b PMP = 4-methoxyphenyl. ^c A 15:1 mixture of *Z/E* isomers was formed. ^d A 4:1 mixture of isomers was formed. ^e Reaction run at 50°C in 1,2-dichloroethane.

In most of the cases studied, the reaction proceeded in a completely selective manner with formation of the (3+2) cycloadducts as the only coupling products. However, in two particular cases involving ethyl 2-diazo-3-methylbut-3-enoate

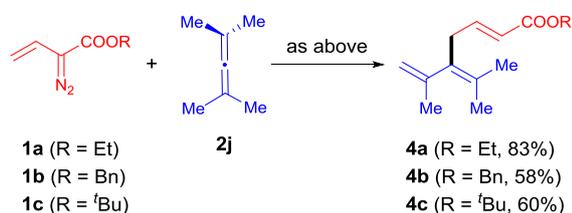
(**1d**) the expected (3+2) cycloadducts were formed along with a side product. Indeed, the reaction of **1d** with 1,1-diphenylallene (**2e**) under the standard conditions led to a separable mixture of the cyclopentene derivative **3p** (30%) and the indene derivative **3p'** (15%). On the other hand, a mixture of **3q** (28%) and triene derivative **3q'** (23%) was formed when the same diazo compound was reacted with vinylidenecyclohexane (**2b**). Interestingly, the configuration of the α,β -unsaturated ester moiety was determined to be *Z* in both side products.

Not only 1,1-disubstituted allenes but also aromatic monosubstituted allenes undergo this gold-catalyzed formal (3+2) cyclization. For example, under standard conditions, reaction of vinyldiazo compound **1a** with phenylpropa-1,2-diene (**2i**) provided an inseparable 4:1 mixture of regioisomers **3u** and **3u'** in a reasonable overall yield (Scheme 1).



Scheme 1. Gold(I)-catalyzed reaction of **1a** with phenylpropa-1,2-diene (**2i**)

Next, a sterically encumbered allene, namely 2,4-dimethyl-2,3-pentadiene (**2j**), was tested to gain insight into the mechanism of the cyclization reaction. Notably, under otherwise identical conditions, the use of this allene did not afford the expected (3+2) cycloadducts. Instead, triene derivatives **4a-c** were isolated as single *E*-isomers in moderate to good yields after chromatographic purification (Scheme 2).



Scheme 2. Gold(I)-catalyzed reaction involving allene **2j**

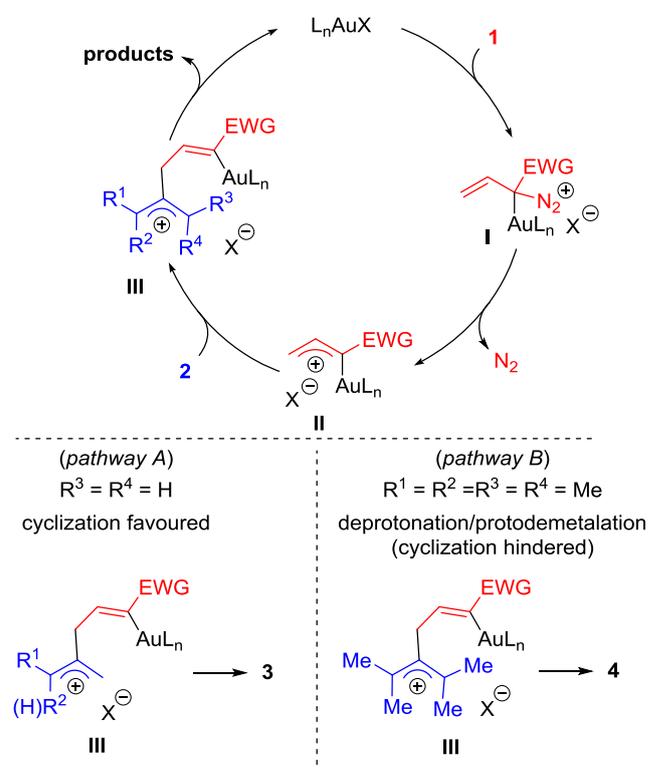
A mechanistic proposal to rationalize the obtained results is depicted in Scheme 3 (see ESI for a preliminary computational study). Initial reaction of the vinyldiazo compound with the gold complex would generate species **I** which would evolve to gold-vinyl carbene intermediate **II** through dinitrogen extrusion.⁹ In agreement with previous reports, this intermediate would show an enhanced vinylogous reactivity. Consequently, nucleophilic attack of the central carbon atom of the allene to this position would form the allyl cation intermediate **III**.¹⁰

The nature of intermediate **III** is thought to play a key role in the reaction outcome. Thus, a cyclization reaction through attack of the vinyl-gold to the allylic moiety would account for the formation of cyclopentene derivatives **3** (*Pathway A*).¹¹ The exquisite regioselective profile of transformations involving 1,1-disubstituted allene derivatives would likely rely on steric reasons with preferential attack to the less substituted carbon

of the allylic moiety. In contrast, in the reaction of phenylpropa-1,2-diene (**2i**), apparently, the presence of only a phenyl group does not provide complete differentiation between both termini of the allylic moiety in the corresponding intermediate **III**. Consequently, cyclization was regioselective, although not exclusive, through the less hindered site of the allylic moiety.

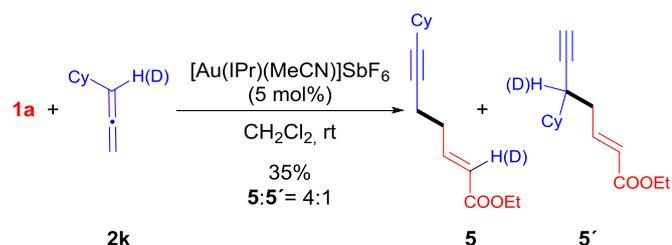
In the case of reactions with 2,4-dimethyl-2,3-pentadiene (**2j**), a completely different evolution of the corresponding intermediate **III** seems to operate. Specifically, a sequence comprising deprotonation/protodemetalation would account for the formation of acyclic derivatives **4** (*Pathway B*). This outcome is very likely related to the increased steric hindrance in the cyclization event. A similar sequence would account for the formation of side product **3q'**.

The formation of indene derivative **3p'** would involve a Nazarov-like cyclization of the corresponding intermediate **III** and subsequent protodemetalation.



Scheme 3. Proposed mechanism

Finally, the reaction of cyclohexylpropa-1,2-diene (**2k**), provided a particularly intriguing outcome. Thus, its treatment with vinyldiazo compound **1a** in the presence of $[\text{Au}(\text{IPr})(\text{CH}_3\text{CN})]\text{SbF}_6$ (5 mol%) resulted in the formation of an inseparable 4:1 mixture of isomeric enynes **5** and **5'** (Scheme 4). An experiment with (1-cyclohexyl-1-deutero)propa-1,2-diene (**[D]-2k**) yielded **[D]-5** with exclusive incorporation of deuterium at the C2 position whereas the deuterium atom was preserved at the C5 position for **[D]-5'**. Although further experiments may be required to clarify this unexpected behaviour, the formation of **5** and **5'** clearly demonstrates that a change in reactivity occurred.

Scheme 4. Gold(I)-catalyzed reaction of **1a** with cyclohexylpropa-1,2-diene (**2k**)

In summary, we have developed new intermolecular coupling reactions of non-activated allenes, challenging substrates in gold-catalyzed cycloaddition reactions. Specifically, the reaction of electronically unbiased disubstituted allene derivatives with vinylidazo compounds afforded five-membered rings arising from a formal (3+2) cycloaddition. To the best of our knowledge, this process represents the first gold-catalyzed intermolecular cyclization involving this type of allene derivatives. These results are consistent with a mechanistic pathway involving initial activation of the vinylidazo coupling partner. However, preliminary experiments involving alkyl monosubstituted allenes suggest that subtle changes in the allene structure may alter notably the chemical behaviour. Further studies on the scope, mechanism and synthetic applications of these new gold-catalyzed transformations are ongoing.

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