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# Gold-catalyzed bicyclic annulations of 4-methoxy-1,2-dienyl-5-ynes with isoxazoles to form indolizine derivatives *via* an Au- $\pi$ -allene intermediate†

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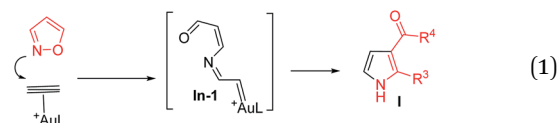
Gold-catalyzed bicyclic annulations of 4-methoxy-1,2-dienyl-5-ynes with isoxazoles afford indolizine derivatives with a structural rearrangement. The mechanism of these new annulations does not involve  $\alpha$ -imino gold carbenes generated from gold  $\pi$ -alkyne intermediates. We postulate alkyne attack on gold  $\pi$ -allenes, yielding vinyl gold carbenes. These newly generated carbenes react with isoxazole derivatives to yield Z-3-imino-2-en-1-als, further enabling sequential cyclizations to deliver indolizine derivatives in two distinct classes.

## Introduction

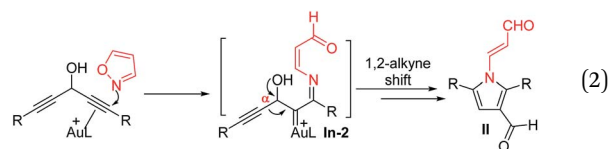
The advent of gold catalysis has greatly promoted the synthetic utility of alkynes. Apart from the functionalizations of alkynes with O, N and C based nucleophiles, gold catalysts also accelerate the development of new alkyne annulations<sup>1</sup> with  $\pi$ -bond motifs. Isoxazoles are readily available aromatic heterocycles; interest in their gold-catalyzed alkyne annulations<sup>2,3</sup> is rapidly growing because of the easy generation of  $\alpha$ -imino gold carbenes (eqn (1)). Ye and coworkers reported the first [3 + 2]-annulations of ynamides with isoxazoles to deliver pyrrole derivatives *via*  $\alpha$ -imino gold carbenes **In-1** (eqn (1)).<sup>3a-c</sup> The use of electron-deficient alkynes also afforded pyrrole products with similar carbene intermediates.<sup>3d</sup> We employed 1,4-diyn-3-ols to seek other azacycles,<sup>4</sup> but still producing pyrrole derivatives *via* a 1,2-alkyne migration to  $\alpha$ -imino gold carbenes (eqn (2)). Despite intensive efforts, the strong preference toward pyrrole products limits the utility of these isoxazole/alkyne annulations. Similar  $\pi$ -alkyne routes were observed for the anthranil/alkyne annulations, yielding indole derivatives.<sup>5</sup> We sought to achieve the synthesis of other azacyclic compounds beyond pyrrole or indole derivatives; generation of intermediates other than  $\alpha$ -imino gold carbenes is a viable route. This work reports gold-catalyzed bicyclic annulations of 4-methoxy-1-allenyl-5-ynes

with isoxazoles to form 8- and 7-formylindolizines **3** and **5**; the structural rearrangement of products is noted here (eqn (3)). We postulate an atypical mechanism for these bicyclic annulations *via* a 1,4-alkyne migration, activated by a gold  $\pi$ -allene intermediate; the resulting vinyl gold carbene **In-3** is trapped by an isoxazole to enable initial sequential cyclizations before delivering indolizine products. This new annulation rationalizes the carbon source of indolizines **3** and **5** from the two reactants well.

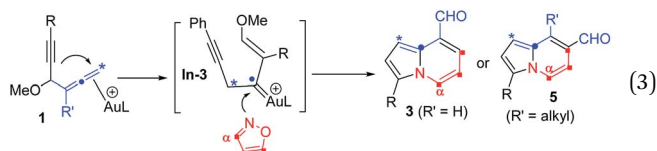
Previous work: gold carbene *via*  $\pi$ -alkyne intermediates



One example:



This work: vinyl gold carbene *via*  $\pi$ -alkyne intermediates

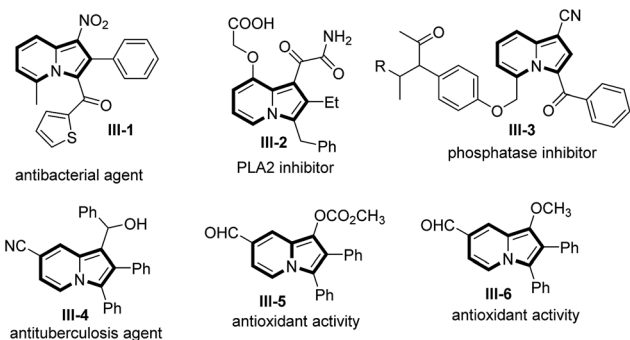


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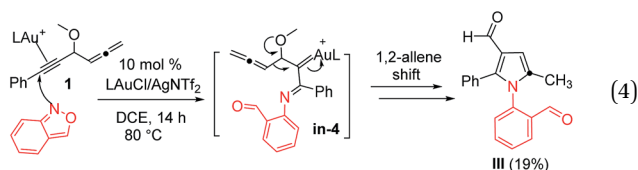
† Electronic supplementary information (ESI) available. CCDC 1894125–1894129 and 1913325. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9sc00735k





Scheme 1 Representative bioactive molecules.

Indolizine frameworks are present in the core structures of natural products including (–)-swainsonine, (+)-castanospermine, lamellarins and camptothecin.<sup>6,7</sup> Synthetic indolizine derivatives, such as compounds **III-1–III-4**, are demonstrated to be antibacterial reagents, PLA2 inhibitors, phosphatase inhibitors and antituberculosis agents<sup>8</sup> whereas species **III-5** and **III-6** show antioxidant activity.<sup>9</sup> Indolizine species **III-5** and **III-6** structurally match with our resulting products **5** bearing a C(7)-aldehyde (Scheme 1).



## Results and discussion

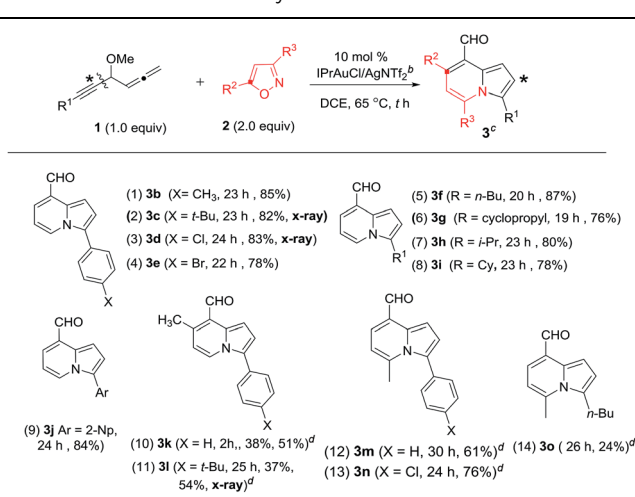
Our initial target focused on the reactions of 4-methoxy-1,2-dienyl-5-ynes **1a** with anthranil using gold catalysts; the reactions gave pyrrole derivatives **III** again (eqn (4)).<sup>10</sup> A mechanistic analysis indicates a typical route of the alkyne activation, involving a 1,2-allene migration to the gold carbene center. We switch our attention to isoxazole derivatives. Table 1 shows the optimizations of a new bicyclic annulation of 4-methoxy-1,2-dienyl-5-yne **1a** with isoxazole **2a** using various gold catalysts. Our initial tests with IPrAuCl/AgNTf<sub>2</sub> (10 mol%) in DCE at 25 °C (27 h) led to a high recovery of the starting alkyne **1a** (entry 1). IPrAuCl/AgNTf<sub>2</sub> (10 mol%) in DCE at 45 °C (48 h) gave unreacted **1a** with a 28% recovery (entry 2). To our pleasure, the reaction in a hot DCE solution (65 °C, 14 h) afforded an indolizine derivative **3a** bearing a C(8)-aldehyde group; the yield was 88% (entry 3). Under these optimized conditions, P(*t*-Bu)<sub>2</sub>(*o*-biphenyl) AuCl/AgNTf<sub>2</sub> was less efficient to yield product **3a** and unreacted **1a** in 62% and 21%, respectively (entry 4). Other gold phosphines such as LAuCl/AgNTf<sub>2</sub> (L = PPh<sub>3</sub>, P(OPh)<sub>3</sub>) were catalytically inactive (entries 5 and 6). Alternations of silver salts as in IPrAuCl/AgX (X = SbF<sub>6</sub> and OTf) rendered the reactions less efficient, giving compounds in 61% and 0%

Table 1 Bicyclic annulations with various gold catalysts<sup>a</sup>

Entry	Catalyst (mol%)	T [°C]	t [h]	Solvent	Yield <sup>b</sup> [%]	
					<b>1a</b>	<b>3a</b>
1	IPrAuCl/AgNTf <sub>2</sub> (10) <sup>c</sup>	25	27	DCE	75	Trace
2	IPrAuCl/AgNTf <sub>2</sub> (10)	45	48	DCE	28	Trace
3	IPrAuCl/AgNTf <sub>2</sub> (10)	65	14	DCE	—	88
4	LAuCl/AgNTf <sub>2</sub> (10) <sup>d</sup>	65	27	DCE	21	62
5	PPh <sub>3</sub> AuCl/AgNTf <sub>2</sub> (10)	65	35	DCE	94	—
6	P(OPh) <sub>3</sub> AuCl/AgNTf <sub>2</sub> (10)	65	32	DCE	95	—
7	IPrAuCl/AgSbF <sub>6</sub> (10)	65	24	DCE	24	61
8	IPrAuCl/AgOTf (10)	65	22	DCE	—	—
9	IPrAuCl (10)	65	13	DCE	85	—
10	AgNTf <sub>2</sub> (10)	65	30	DCE	76	—
11	IPrAuCl/AgNTf <sub>2</sub> (10)	65	25	THF	—	—
12	IPrAuCl/AgNTf <sub>2</sub> (10)	80	21	MeCN	87	—
13	IPrAuCl/AgNTf <sub>2</sub> (10)	100	21	Toluene	—	Trace

<sup>a</sup> [1a] = 0.15 M. <sup>b</sup> Product yields are reported after separation from a silica column. <sup>c</sup> IPr = 1,3-bis(diisopropylphenyl)imidazole-2-ylidene. <sup>d</sup> L = P(*t*-Bu)<sub>2</sub>(*o*-biphenyl), DCE = 1,2-dichloroethane, DCM = dichloromethane, THF = tetrahydrofuran, MeCN = acetonitrile, Tf = trifluoromethanesulfonyl.

yields respectively; the reactions were only compatible with non-coordinating anions (entries 7 and 8). IPrAuCl or AgNTf<sub>2</sub> alone (10 mol%) was entirely inactive (entries 9 and 10). IPrAuCl/AgNTf<sub>2</sub> became inefficient in THF, MeCN and toluene (entries 11–13). The structure of compound **3a** was

Table 2 Formation of 8-formylindolizines<sup>a</sup>

<sup>a</sup> [1] = 0.15 M. <sup>b</sup> IPr = 1,3-bis(diisopropylphenyl)imidazole-2-ylidene. <sup>c</sup> Product yields are reported after separation from a silica column. <sup>d</sup> These data correspond to 3 equiv. of isoxazole, Tf = trifluoromethanesulfonyl.



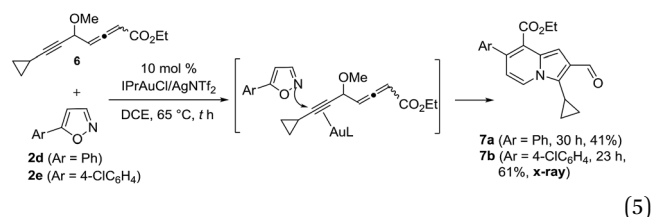
inferred from X-ray diffraction studies of its related compounds **3c** and **3d**,<sup>11</sup> as depicted in Table 2, and further verified with <sup>1</sup>H NOE spectra.

We assessed the generality of these bicyclic annulations with various 4-methoxy-1,2-dienyl-5-ynes and substituted isoxazoles; the results are depicted in Table 2. We tested these annulations first on 4-phenylethynyl allene substrates **1b–1e** (X = Me, *tert*-butyl, Cl and Br), smoothly affording 8-formylindolizine derivatives **3b–3e** in good yields (78–85%, entries 1–4); X-ray diffraction revealed that products **3c** and **3d** bear an aldehyde at their C(8)-carbons. The reactions were further compatible with alkylethynyl allenes **1f–1i** (R = *n*-butyl, cyclopropyl, isopropyl and cyclohexyl), yielding desired indolizines **3f–3i** in 76–87% (entries 5–8). For 2-naphthylethynyl allene **1j**, its corresponding indolizine **3j** was obtained in 84% yield (entry 9). We performed the reaction on 5-methylisoxazole **2b** (R<sup>2</sup> = Me), yielding 7-methyl-8-formylindolizines **3k** and **3l** in 38% and 37% yields, respectively (entries 10 and 11); the yields of the two products were increased to 51% and 54% using a high loading of isoxazole **2b** (3 equiv.). The molecular structure of indolizine **3l** was confirmed with X-ray diffraction.<sup>11</sup> For 3-methylisoxazole **2c** (R<sup>3</sup> = Me), its corresponding indolizines **3m** and **3n** were obtained in 61% and 76% yields respectively (entries 12 and 13); the proposed structure of **3m** was verified by <sup>1</sup>H NOE spectra. We tested the reactions on an alkyl-substituted allene substrate with **2c** rendered desired **3o** with 24% yield (entry 14). Structural analysis of these indolizine products supports a 1,4-migration of the alkynyl moiety to the C(1)-allene carbon.

As depicted in Table 3, 3-disubstituted allene derivatives **4** gave distinct 7-formylindolizines **5** under the same conditions. We assessed the scope of this new annulation using various allenynes bearing R<sup>1</sup> and R<sup>2</sup> substituents. Entries 1–3 show the applicability of this catalysis to various phenylethynyl allenes **4a–4c** (X = H, Cl and Br), rendering the desired

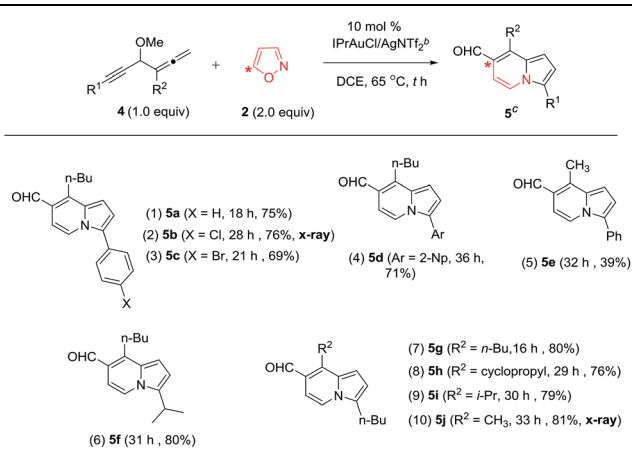
products **5a–5c** in 69–76% yields (entries 1–3); the molecular structure of the chloro derivative **5b** was determined with X-ray diffraction.<sup>11</sup> For 2-naphthylethynyl allene **4d**, its corresponding product **5d** was obtained in 71% yield (entry 4). The reaction was extensible to substrate **4e** bearing 3-methylallene (R<sup>2</sup> = Me), yielding compound **5e** in 39% yield (entry 5). We tested the reactions on all alkyl-substituted 1,2-dienyl-5-allenes **4f–4j** (R<sup>1</sup>, R<sup>2</sup> = alkyl), delivering the desired 7-formylindolizines **5f–5j** in satisfactory yields (76–81%, entries 6–10). The proposed structure of compound **5j** was confirmed with X-ray diffraction study.<sup>11</sup>

To test the electronic effect of allenyl substituents, we prepared an allenyl ester **6** that reacted with 5-arylisoxazoles **2d** (Ar = Ph) and **2e** (Ar = 4-ClPh) to yield indolizine derivatives **7a** and **7b** (eqn (5)). The X-ray diffraction results of compound **7b** confirmed its structure with no 1,4-alkyne shift; the formation of these two products arose from gold  $\pi$ -alkyne intermediates as described before (eqn (4)). The change of chemoselectivity is attributed to a weak coordination between gold and an allenyl ester.



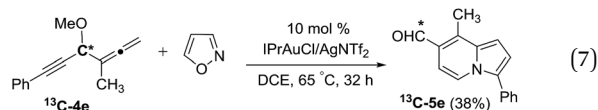
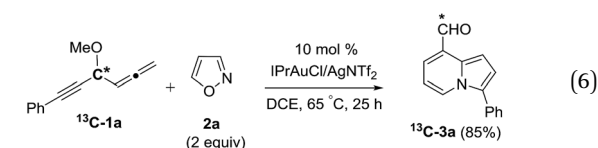
We performed a series of experiments to elucidate the mechanisms of formation of 8- and 7-formylindolizines **3** and **5**. We prepared <sup>13</sup>C-enriched **1a** and **4e**; each contained 10% <sup>13</sup>C content in the CH-OMe carbon. Their resulting products <sup>13</sup>C-**3a** and <sup>13</sup>C-**5e** were found to have the enrichment at the aldehyde carbons (eqn (6) and (7)). We prepared d<sub>2</sub>-**1a** bearing =CD<sub>2</sub> at the allene C(1)-carbon; its resulting indolizine d<sub>2</sub>-**3a** comprised equal deuterium content (X = Y = 0.72 D) at the two pyrrolyl carbons. We also performed a crossover experiment involving d<sub>2</sub>-**1a** and d<sub>0</sub>-**1b**; this mixture only produced d<sub>2</sub>-**3a** and d<sub>0</sub>-**3b** according to the mass analysis. The entire 1,2-dienyl-5-yne skeleton **1** remained completely on the resulting indolizine molecule.

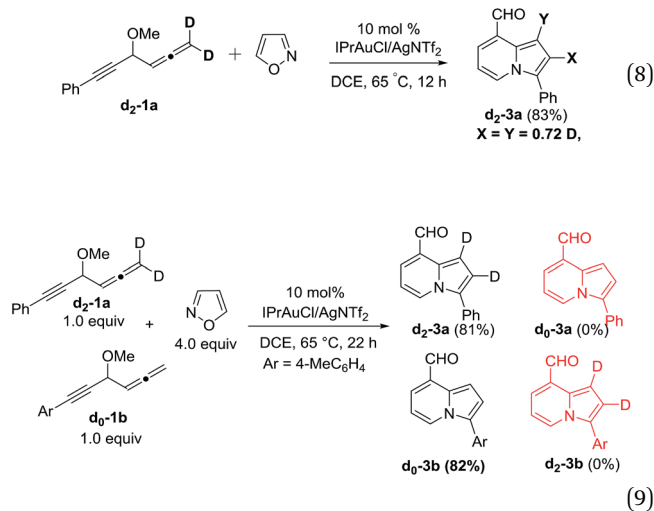
Table 3 Formation of 7-formylindolizines<sup>a</sup>



<sup>a</sup> [4] = 0.15 M. <sup>b</sup> IPr = 1,3-bis(diisopropylphenyl)imidazole-2-ylidene.

<sup>c</sup> Product yields are reported after separation from a silica column.

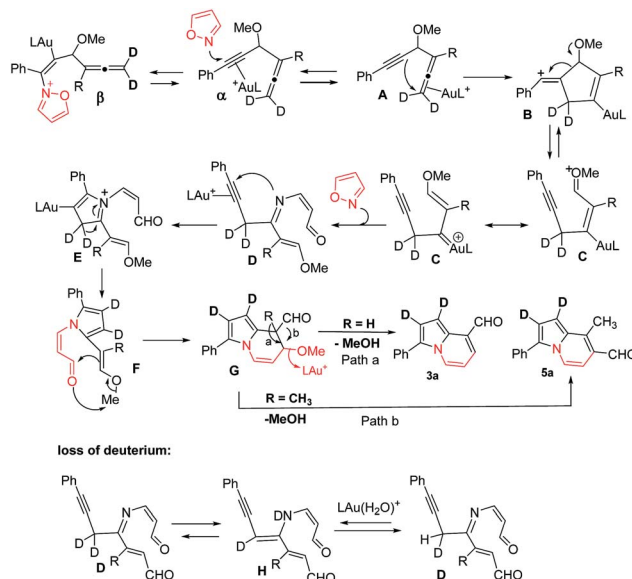




According to the structural analysis of the resulting indolizines **3** and **5**, we postulate a mechanism involving an allene-activation route. This mechanism rationalizes the deuterium and crossover experiments well (eqn (8) and (9)). We use  $d_2$ -1a ( $R = H$ ) as a tool to verify the mechanism. In the N-attack of isoxazole **2a** with Au- $\pi$ -alkyne  $\alpha$ , the resulting intermediate  $\beta$  has a highly aromatic isoxazole ring that is difficult to cleave. We postulate an alternative path involving nucleophilic attack of an alkyne at its tethered Au- $\pi$ -allene **A** to form vinyl cation **B**. An alkyne as a nucleophile to attack an electrophilic Au- $\pi$ -allene is noted in gold catalysis.<sup>12</sup> We conceive that this vinyl cation induces a subsequent C-C bond cleavage of species **B** to form phenylalkyne species **C** bearing an allyl cation **C**, as stabilized by the gold and methoxy group. This species has a resonance form of vinyl gold carbene that reacts smoothly with isoxazole to yield a 3-imino-2-en-1-al **D** with *Z*-configuration.<sup>13</sup> An amination on the alkyne of species **D** is expected to form an azacyclic intermediate **E** which leads to the desired pyrrole intermediate **F**. For mono-substituted allenes **1** ( $R = H$ ), a further carbonyl-ene reaction of species **F** yields pyrrole-fused six-membered species **G**, which loses MeOH to yield 8-formyl indolizine **3a**. In the case of a 3,3-disubstituted allene **4** ( $R = \text{alkyl}$ ), a 1,2-formyl shift to the neighboring carbocation occurs preferentially to give 7-formyl indolizine derivative **5a** (Scheme 2).

This postulated mechanism rationalizes a small loss of deuterium content of the indolizine product  $d_2$ -3a ( $X = Y = 0.72 D$ ), as depicted in eqn (8). In the hot DCE solution (65 °C 12 h), an imine-enamine tautomerization, as shown by species **D** and **H**, results in a deuterium loss of species **D** because of an exchange with residual water. In this mechanism, a major concern is the cleavage of the sigma C-C bond of species **B** to yield vinyl gold carbene **C**.

Calculations with density functional theory (B3LYP) were performed to support our proposed mechanism. Attention was paid to the transformations of the gold  $\pi$ -allene intermediate **A** (Fig. 1) to gold pyrrolium (**F**), since the last few steps are well known in organic reactions. 1,4-Alkyne



Scheme 2 A proposed mechanism.

migration of **A** to form **C** is a stepwise process: transformation **A**  $\rightarrow$  **B** occurs with  $\Delta H^\ddagger/\Delta H = 11.0/-0.7$  kcal mol<sup>-1</sup>; cleavage of the C-C bond of species **B** results in the formation of intermediate **C** with  $\Delta H^\ddagger/\Delta H = 5.7/-7.3$  kcal mol<sup>-1</sup>. Species **C** is subsequently attacked by an isoxazole to generate **C'** with  $\Delta H^\ddagger/\Delta H = 11.1/1.0$  kcal mol<sup>-1</sup>. Next, the ligation of another IPrAu<sup>+</sup> to species **C'** is expected to form a digold species **C''** with  $\Delta H = -13.4$  kcal mol<sup>-1</sup>; this process is accompanied by a N-O cleavage of the isoxazole moiety of species **C''** to generate **D'** with  $\Delta H^\ddagger/\Delta H = 5.7/-21.8$  kcal mol<sup>-1</sup>. Finally, a release of IPrAu<sup>+</sup> from species **D'** eventually yields a gold- $\pi$ -alkyne **D** with  $\Delta H = -4.2$  kcal mol<sup>-1</sup>; an intramolecular cyclization of species **D** generates gold-containing pyrrolium species **F** with no kinetic barrier and  $\Delta H = -21.1$  kcal mol<sup>-1</sup>. In this **D**  $\rightarrow$  **F** step, the electronic barrier is 0.01 kcal mol<sup>-1</sup>, which disappears after correction for zero-point energy. Overall, all the kinetic barriers are less than 11.1 kcal mol<sup>-1</sup> with all the steps being thermodynamically downhill except the step **C**  $\rightarrow$  **C'** ( $\Delta H = +1.0$  kcal mol<sup>-1</sup>). The entire reaction (**A**  $\rightarrow$  **F**) releases an enthalpy -67.5 kcal mol<sup>-1</sup>. Our calculations thus show that the entire process is kinetically facile and thermodynamically favorable, verifying the proposed mechanism.

We also perform the calculation on a competitive reaction involving gold  $\pi$ -alkyne intermediates  $\alpha$ , which has energy 1.3 kcal mol<sup>-1</sup> greater than that of the gold  $\pi$ -allene (**A**). The attack of an isoxazole on  $\pi$ -alkyne  $\alpha$  generated alkenylgold species  $\beta$  with  $\Delta H^\ddagger/\Delta H = 13.0/3.5$  kcal mol<sup>-1</sup>. This was followed by a ring-opening reaction to form  $\alpha$ -imino gold carbene  $\gamma$  with  $\Delta H^\ddagger/\Delta H = 4.9/-8.9$  kcal mol<sup>-1</sup>. Notably, the barrier for formation and the energy state of intermediate  $\beta$  are greater than those of all intermediates in the  $\pi$ -allene route. We conclude that this  $\pi$ -alkyne route is unlikely to play an important role in the reaction.





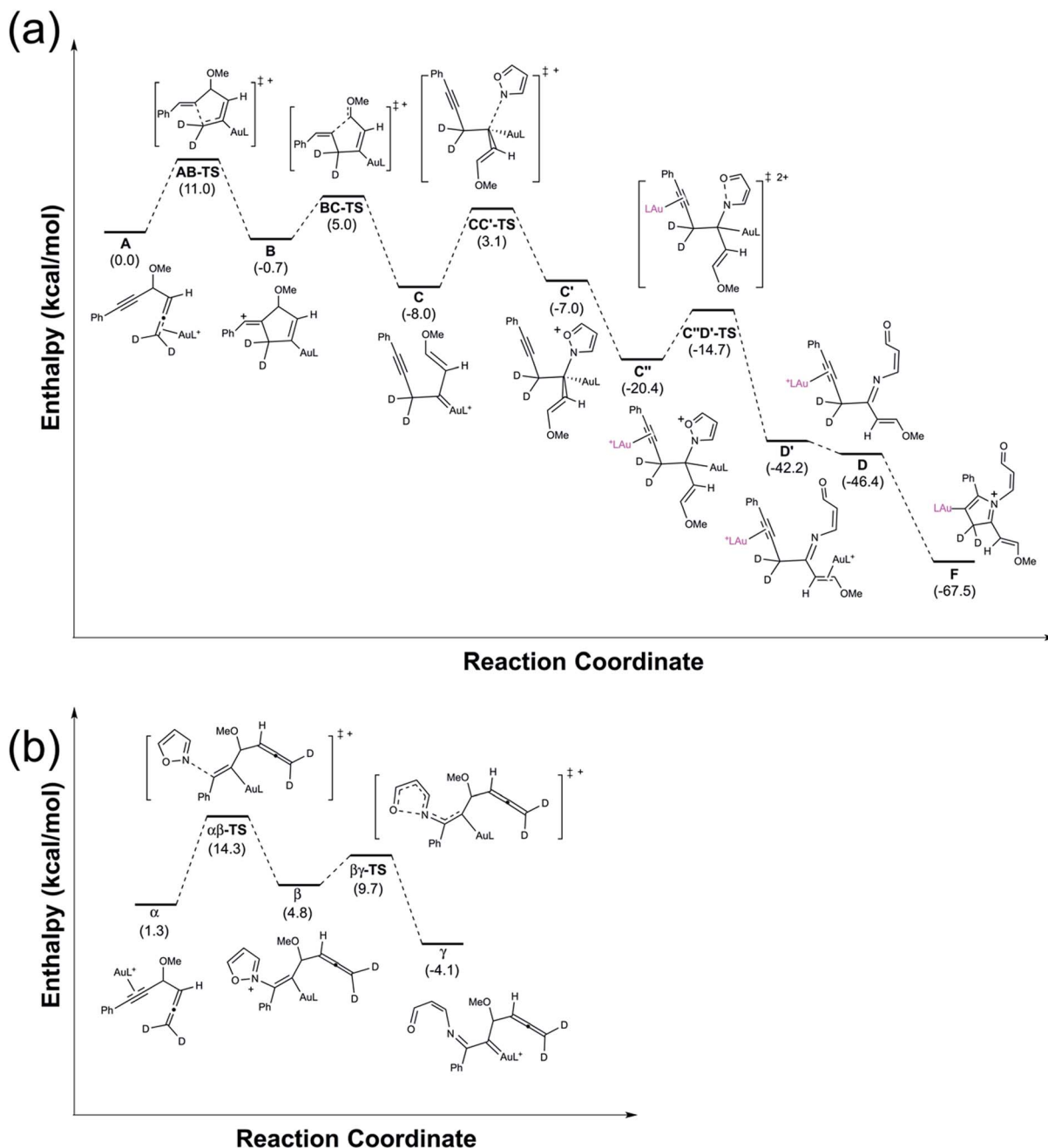


Fig. 1 The enthalpic energy profile calculated using density functional theory.

## Conclusions

In summary, we report new gold-catalyzed bicyclic annulations between 4-methoxy-1,2-dienyl-5-ynes and isoxazoles to form 7- and 8-formyl indolizine derivatives.<sup>13</sup> This reaction process does not follow a typical  $\pi$ -alkyne route;  $\alpha$ -imino gold carbenes<sup>14,15</sup> do not form here. Instead, the mechanism involves  $\pi$ -allene intermediates to induce a 1,4-alkyne shift, yielding a vinyl gold carbene **C** that is trapped with an isoxazole to generate an  $\alpha$ -imino-2-en-1-ol. Gold-catalyzed sequential cyclizations of this imine intermediate enable the construction of an indolizine skeleton. This mechanism rationalizes the isotope labeling and crossover

experiments well. New versions for these gold-catalyzed annulations will be helpful for the design of new catalysis.

## Conflicts of interest

There are no conflicts of interest to declare.

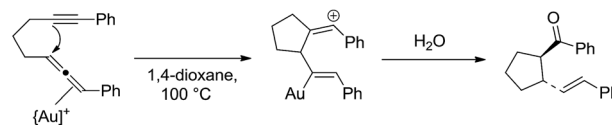
## Acknowledgements

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