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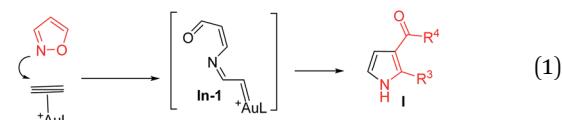
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Introduction

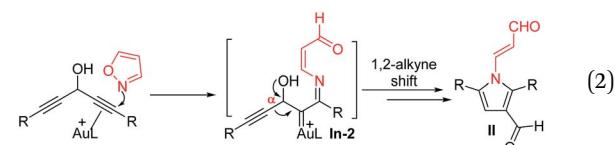
The advent of gold catalysis has greatly promoted the synthetic utility of alkynes. Apart from the functionalizations of alkynes with O, N and C based nucleophiles, gold catalysts also accelerate the development of new alkyne annulations¹ with π -bond motifs. Isoxazoles are readily available aromatic heterocycles; interest in their gold-catalyzed alkyne annulations^{2,3} is rapidly growing because of the easy generation of α -imino gold carbenes (eqn (1)). Ye and coworkers reported the first [3 + 2]-annulations of ynamides with isoxazoles to deliver pyrrole derivatives via α -imino gold carbenes **In-1** (eqn (1)).^{3a-c} The use of electron-deficient alkynes also afforded pyrrole products with similar carbene intermediates.^{3d} We employed 1,4-dien-3-ols to seek other azacycles,⁴ but still producing pyrrole derivatives via a 1,2-alkyne migration to α -imino gold carbenes (eqn (2)). Despite intensive efforts, the strong preference toward pyrrole products limits the utility of these isoxazole/alkyne annulations. Similar π -alkyne routes were observed for the anthranil/alkyne annulations, yielding indole derivatives.⁵ We sought to achieve the synthesis of other azacyclic compounds beyond pyrrole or indole derivatives; generation of intermediates other than α -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 π -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.

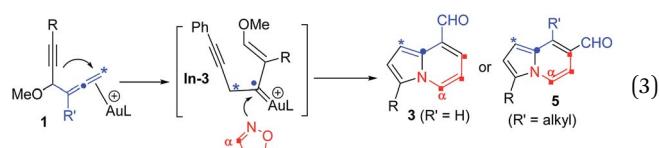
Previous work: gold carbene via π -alkyne intermediates



One example:



This work: vinyl gold carbene via π -alkyne intermediates

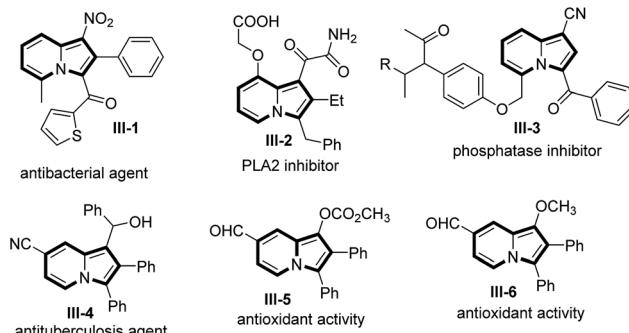


^aFrontier Research Centers on Fundamental and Applied Science of Matters, Department of Chemistry, National Tsing-Hua University, Hsinchu, Taiwan, Republic of China. E-mail: rsliu@mx.nthu.edu.tw

^bDepartment of Chemistry, National Cheng Kung University, Tainan 701, Taiwan. E-mail: mjcheng@mail.ncku.tw

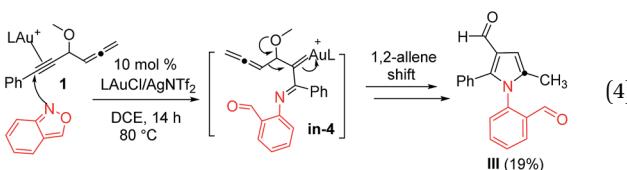
[†] Electronic supplementary information (ESI) available. CCDC 1894125–1894129 and 1913325. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9sc00735k





Scheme 1 Representative bioactive molecules.

Indolizine frameworks are present in the core structures of natural products including (–)-swainsonine, (+)-castanospermine, lamellarins and camptothecin.^{6,7} Synthetic indolizine derivatives, such as compounds III-1–III-4, are demonstrated to be antibacterial reagents, PLA2 inhibitors, phosphatase inhibitors and antituberculosis agents⁸ whereas species III-5 and III-6 show antioxidant activity.⁹ 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)).¹⁰ 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/AgNTf₂ (10 mol%) in DCE at 25 °C (27 h) led to a high recovery of the starting alkyne **1a** (entry 1). IPrAuCl/AgNTf₂ (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)₂(*o*-biphenyl) AuCl/AgNTf₂ was less efficient to yield product **3a** and unreacted **1a** in 62% and 21%, respectively (entry 4). Other gold phosphines such as LAuCl/AgNTf₂ (*L* = PPh₃, P(OPh)₃) were catalytically inactive (entries 5 and 6). Alternations of silver salts as in IPrAuCl/AgX (X = SbF₆ and OTf) rendered the reactions less efficient, giving compounds in 61% and 0%

Table 1 Bicyclic annulations with various gold catalysts^a

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

^a [1a] = 0.15 M. ^b Product yields are reported after separation from a silica column. ^c IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene.

^d L = P(t-Bu)₂(*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 AgNTf₂ alone (10 mol%) was entirely inactive (entries 9 and 10). IPrAuCl/AgNTf₂ became inefficient in THF, MeCN and toluene (entries 11–13). The structure of compound **3a** was

Table 2 Formation of 8-formylindolizines^a

$\begin{array}{c} \text{OMe} \\ \\ \text{R}^1-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{R}^1 \end{array}$		$\begin{array}{c} \text{R}^2-\text{O}-\text{N}=\text{O} \\ \\ \text{R}^3 \end{array}$	$\begin{array}{c} \text{R}^2-\text{O}-\text{C}=\text{C}-\text{N}=\text{C}-\text{R}^3 \\ \\ \text{R}^1 \end{array}$
1 (1.0 equiv)	2 (2.0 equiv)	10 mol % IPrAuCl/AgNTf ₂ ^b DCE, 65 °C, t h	$\begin{array}{c} \text{CHO} \\ \\ \text{R}^2-\text{C}=\text{C}-\text{N}=\text{C}-\text{R}^3 \\ \\ \text{R}^1 \end{array}$
(1) 3b (X = CH ₃ , 23 h, 85%)	(2) 3c (X = t-Bu, 23 h, 82%, x-ray)	(5) 3f (R = <i>n</i> -Bu, 20 h, 87%)	
(3) 3d (X = Cl, 24 h, 83%, x-ray)	(6) 3g (R = cyclopropyl, 19 h, 76%)	(7) 3h (R = <i>i</i> -Pr, 23 h, 80%)	
(4) 3e (X = Br, 22 h, 78%)	(8) 3i (R = Cy, 23 h, 78%)	(9) 3j (Ar = 2-Np, 24 h, 84%)	
		(10) 3k (X = H, 2 h, 38%, 51%) ^d	(11) 3l (X = t-Bu, 25 h, 37%, 54%, x-ray) ^d
		(12) 3m (X = H, 30 h, 61%) ^d	(13) 3n (X = Cl, 24 h, 76%) ^d
		(14) 3o (26 h, 24%) ^d	

^a [1] = 0.15 M. ^b IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene.

^c Product yields are reported after separation from a silica column.

^d These data correspond to 3 equiv. of isoxazole, Tf = trifluoromethanesulfonyl.



inferred from X-ray diffraction studies of its related compounds **3c** and **3d**,¹¹ as depicted in Table 2, and further verified with ¹H 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** ($X = \text{Me}$, *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** ($R = n\text{-butyl}$, 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** ($R^3 = \text{Me}$), 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.¹¹ For 3-methylisoxazole **2c** ($R^3 = \text{Me}$), 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 ¹H 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^1 and R^2 substituents. Entries 1–3 show the applicability of this catalysis to various phenylethynyl allenes **4a–4c** ($X = \text{H}$, 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.¹¹ 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 ($R^2 = \text{Me}$), yielding compound **5e** in 39% yield (entry 5). We tested the reactions on all alkyl-substituted 1,2-dienyl-5-allenes **4f–4j** ($R^1, R^2 = \text{alkyl}$), 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.¹¹

To test the electronic effect of allenyl substituents, we prepared an allenyl ester **6** that reacted with 5-aryl(isoxazoles **2d** ($\text{Ar} = \text{Ph}$) and **2e** ($\text{Ar} = 4\text{-ClPh}$) 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 π -alkyne intermediates as described before (eqn (4)). The change of chemoselectivity is attributed to a weak coordination between gold and an allenyl ester.

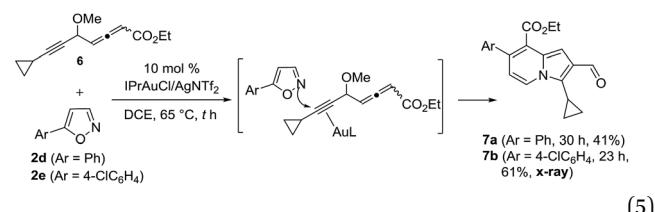


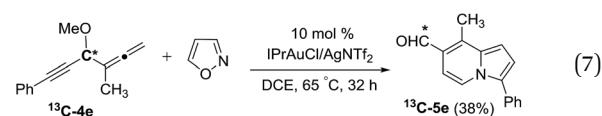
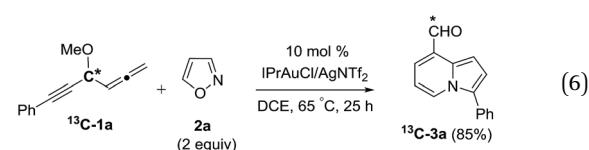
Table 3 Formation of 7-formylindolizines^a

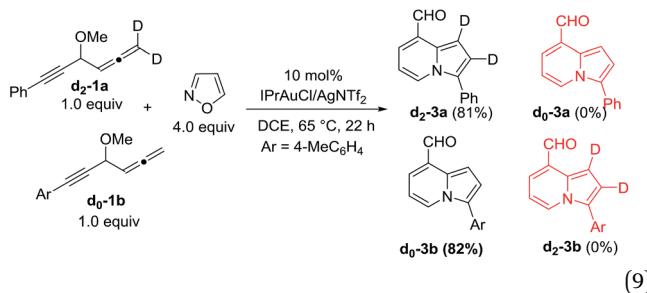
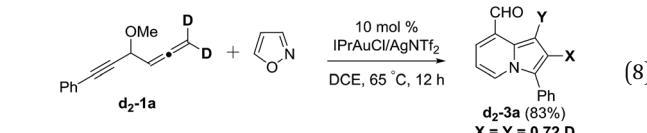
4 (1.0 equiv)	2 (2.0 equiv)	10 mol % IPrAuCl/AgNTf ₂ ^b DCE, 65 °C, t h
(1) 5a ($X = \text{H}$, 18 h, 75%)		
(2) 5b ($X = \text{Cl}$, 28 h, 76%, x-ray)		
(3) 5c ($X = \text{Br}$, 21 h, 69%)		
	(4) 5d ($\text{Ar} = 2\text{-Np}$, 36 h, 71%)	
	(5) 5e (32 h, 39%)	
	(6) 5f (31 h, 80%)	
	(7) 5g ($R^2 = n\text{-Bu}$, 16 h, 80%)	
	(8) 5h ($R^2 = \text{cyclopropyl}$, 29 h, 76%)	
	(9) 5i ($R^2 = i\text{-Pr}$, 30 h, 79%)	
	(10) 5j ($R^2 = \text{CH}_3$, 33 h, 81%, x-ray)	

^a [4] = 0.15 M. ^b IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene.

^c Product yields are reported after separation from a silica column.

We performed a series of experiments to elucidate the mechanisms of formation of 8- and 7-formylindolizines **3** and **5**. We prepared ¹³C-enriched **1a** and **4e**; each contained 10% ¹³C content in the CH-OMe carbon. Their resulting products ¹³C-**3a** and ¹³C-**5e** were found to have the enrichment at the aldehyde carbons (eqn (6) and (7)). We prepared **d₂-1a** bearing =CD₂ at the allene C(1)-carbon; its resulting indolizine **d₂-3a** comprised equal deuterium content ($X = Y = 0.72$ D) at the two pyrrolyl carbons. We also performed a crossover experiment involving **d₂-1a** and **d₀-1b**; this mixture only produced **d₂-3a** and **d₀-3b** according the mass analysis. The entire 1,2-dienyl-5-yne skeleton **1** remained completely on the resulting indolizine molecule.

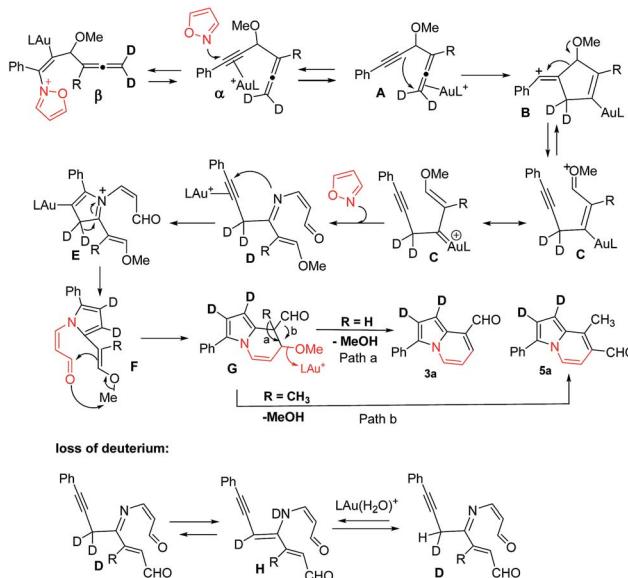




According to the structural analysis of the resulting indolizines 3 and 5, we postulate a mechanism involving an allene-activation route. This mechanism rationalizes the deuterium and crossover experiments well (eqn (8) and (9)). We use **d₂-1a** (R = H) as a tool to verify the mechanism. In the N-attack of isoxazole **2a** with Au- π -alkyne α , the resulting intermediate β 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- π -allene **A** to form vinyl cation **B**. An alkyne as a nucleophile to attack an electrophilic Au- π -allene is noted in gold catalysis.¹² 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.¹³ 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 = 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 **d₂-3a** (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 π -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⁻¹; 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⁻¹. Species **C** is subsequently attacked by an isoxazole to generate **C'** with $\Delta H^\ddagger/\Delta H = 11.1/1.0$ kcal mol⁻¹. Next, the ligation of another IPrAu⁺ to species **C'** is expected to form a digold species **C''** with $\Delta H = -13.4$ kcal mol; 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⁻¹. Finally, a release of IPrAu⁺ from species **D'** eventually yields a gold- π -alkyne **D** with $\Delta H = -4.2$ kcal mol; an intramolecular cyclization of species **D** generates gold-containing pyrrolium species **F** with no kinetic barrier and $\Delta H = -21.1$ kcal mol⁻¹. In this **D** \rightarrow **F** step, the electronic barrier is 0.01 kcal mol⁻¹, which disappears after correction for zero-point energy. Overall, all the kinetic barriers are less than 11.1 kcal mol⁻¹ with all the steps being thermodynamically downhill except the step **C** \rightarrow **C'** ($\Delta H = +1.0$ kcal mol⁻¹). The entire reaction (**A** \rightarrow **F**) releases an enthalpy -67.5 kcal mol⁻¹. 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 π -alkyne intermediates α , which has energy 1.3 kcal mol⁻¹ greater than that of the gold π -allene (**A**). The attack of an isoxazole on π -alkyne α generated alkenylgold species **β** with $\Delta H^\ddagger/\Delta H = 13.0/3.5$ kcal mol⁻¹. This was followed by a ring-opening reaction to form α -imino gold carbene γ with $\Delta H^\ddagger/\Delta H = 4.9/-8.9$ kcal mol⁻¹. Notably, the barrier for formation and the energy state of intermediate β are greater than those of all intermediates in the π -allene route. We conclude that this π -alkyne route is unlikely to play an important role in the reaction.



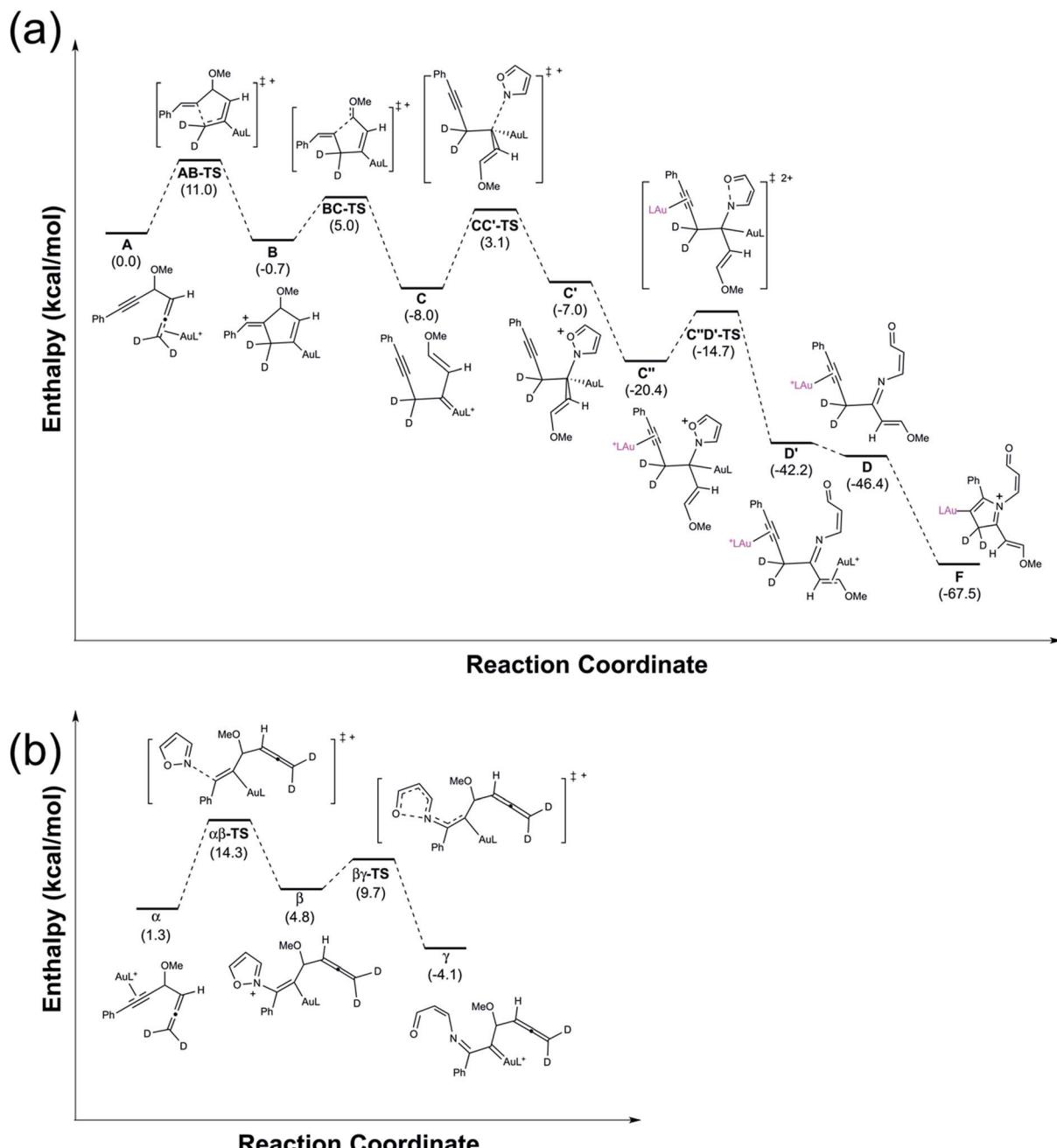


Fig. 1 The enthalpic energy profile calculated using density functional theory.

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.¹³ This reaction process does not follow a typical π -alkyne route; α -imino gold carbenes^{14,15} do not form here. Instead, the mechanism involves π -allene intermediates to induce a 1,4-alkyne shift, yielding a vinyl gold carbene C that is trapped with an isoxazole to generate an α -imino-2-en-1-al. 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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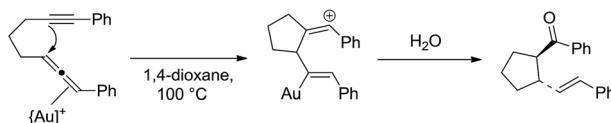
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11 Crystallographic data of compounds **3c**, **3d**, **3l**, **5b**, **5j** and **7b** were deposited at Cambridge Crystallographic Data Center: **3c** (CCDC 1894127), **3d** (CCDC 1894128), **3l** (CCDC 1894129), **5b** (CCDC 1894126), **5j** (CCDC 1894125) and **7b** (CCDC 1913325).†

12 We recently reported nucleophilic attack of an alkyne at a gold-π-allene to yield a vinyl cation that was trapped with water; the reaction scheme is shown below. Our proposed mechanism is similar to this process. See: C.-Y. Yang, G.-Y. Lin, H.-Y. Liao, S. Datta and R.-S. Liu, *J. Org. Chem.*, 2008, **73**, 4907.



13 For the reactions of isoxazoles and gold carbenes, see a recent example: B. D. Mokar, P. D. Jadhav, Y. B. Pandit and R.-S. Liu, *Chem. Sci.*, 2018, **9**, 4488.

14 (a) D. G. Hulcoop and M. Lautens, *Org. Lett.*, 2007, **9**, 1761; (b) F.-S. Wu, H.-Y. Zhao, Y.-L. Xu, K. Hu, Y.-M. Pan and X.-L. Ma, *J. Org. Chem.*, 2017, **82**, 4289; (c) C.-L. Ma, J.-H. Zhao, Y. Yang, M.-K. Zhang, C. Shen, R. Sheng, X.-W. Dong and Y.-Z. Hu, *Sci. Rep.*, 2017, **7**, 16640; (d) S. Teklu, L.-L. Gundersen, T. Larsen, K. E. Malterud and F. Rise, *Bioorg. Med. Chem. Lett.*, 2005, **13**, 3127.

15 For generation of α -imino gold carbenes with other nitrene sources, see selected examples: (a) R. J. Reddy, M. P. B. Jones and P. W. Davies, *Angew. Chem., Int. Ed.*, 2017, **56**, 13310; (b) P. W. Davies, A. Cremonesi and L. Dumitrescu, *Angew. Chem., Int. Ed.*, 2011, **50**, 8931; (c) E. Chatzopoulou and P. W. Davies, *Chem. Commun.*, 2013, **49**, 8617; (d) L. Zhu, Y. Yu, Z. Mao and X. Huang, *Org. Lett.*, 2015, **17**, 30; (e) S. K. Pawar, R. L. Sahani and R. S. Liu, *Chem.-Eur. J.*, 2015, **21**, 10843.

