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Computational insights into the mechanisms and origins of switchable selectivity in gold(I)-catalyzed annulation of ynamides with isoxazoles *via* 6π-electrocyclizations of azaheptatrienyl cations†

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Electrocyclizations of acyclic conjugated π-motifs have emerged as a versatile and effective strategy for accessing various ring systems with excellent functional group tolerability and controllable selectivity. Typically, the realization of 6π-electrocyclization of heptatrienyl cations to afford seven-membered motif has proven difficult due to the high-energy state of the cyclizing seven-membered intermediate. Instead, it undergoes the Nazarov cyclization, affording a five-membered pyrrole product. However, the incorporation of a Au(I)-catalyst, a nitrogen atom and tosylamide group in the heptatrienyl cations unexpectedly circumvented the aforementioned high energy state to afford a seven-membered azepine product *via* 6π-electrocyclization in the annulation of 3-en-1-ynamides with isoxazoles. Therefore, extensive computational studies were carried out to investigate the mechanism of Au(I)-catalyzed [4+3] annulation of 3-en-1-ynamides with dimethylisoxazoles to produce a seven-membered 4*H*-azepine *via* the 6π-electrocyclization of azaheptatrienyl cations. Computational results showed that after the formation of the key α-imino gold carbene intermediate, the annulation of 3-en-1-ynamides with dimethylisoxazole occurs *via* the unusual 6π-electrocyclization to afford a seven-membered 4*H*-azepine exclusively. However, the annulation of 3-cyclohexen-1-ynamides with dimethylisoxazole occurs *via* the commonly proposed aza-Nazarov cyclization pathway to majorly generate five-membered pyrrole derivatives. The results from the DFT predictive analysis revealed that the key factors responsible for the different chemo-, and regio-selectivities observed are the cooperating effect of the tosylamide group on C^1, the uninterrupted π-conjugation pattern of the α-imino gold(I) carbene and the substitution pattern at the cyclization termini. The Au(I)-catalyst is believed to assist in the stabilization of the azaheptatrienyl cation.

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Introduction

Recent advances in gold catalysis have inspired new annulations between alkynes and nucleophiles toward the synthesis of rings and ring systems with excellent functional group tolerability and controllable selectivity.[1–8] Among the alkynes, significant attention has been paid to annulation involving ynamides due to the highly electrophilic keteniminium nature exhibited by their Au-π-alkyne complexes, as well as their higher reactivity compared to normal alkynes.[2–8] In this regard, the annulation of ynamides with nucleophiles[3–8] including isoxazoles[5f,6-8] is one of the most powerful ring-forming strategies to assemble valuable azacyclic frameworks which are core structures found in myriads of natural products, bioactive molecules and pharmaceuticals.[3–8] Since the seminal work reported by Ye and co-workers[6a] in 2015 to access various polysubstituted 2-aminopyrroles *via* the gold-catalyzed [3+2] annulation of ynamides with isoxazoles, several annulations involving ynamides and isoxazoles with its derivatives have been developed.[6–8] For instance, Hashmi and co-workers[6c] elegantly revealed the Au(I)-catalyzed [3+2] annulation of ynamides with benzisoxazoles to deliver a facile, flexible, and atom-economical one-step route to unprotected 7-acylindoles. Furthermore, Gandon and Sahoo[5f] reported the combined experimental and DFT studies on the ring expansion and 1,2-migration cascade of benzisoxazoles with ynamides to produce benzo[e][1,3]oxazine of predominant *E* configuration. More recently, Hu *et al.*[6g] provided a comprehensive summary of the annulations involving ynamides and

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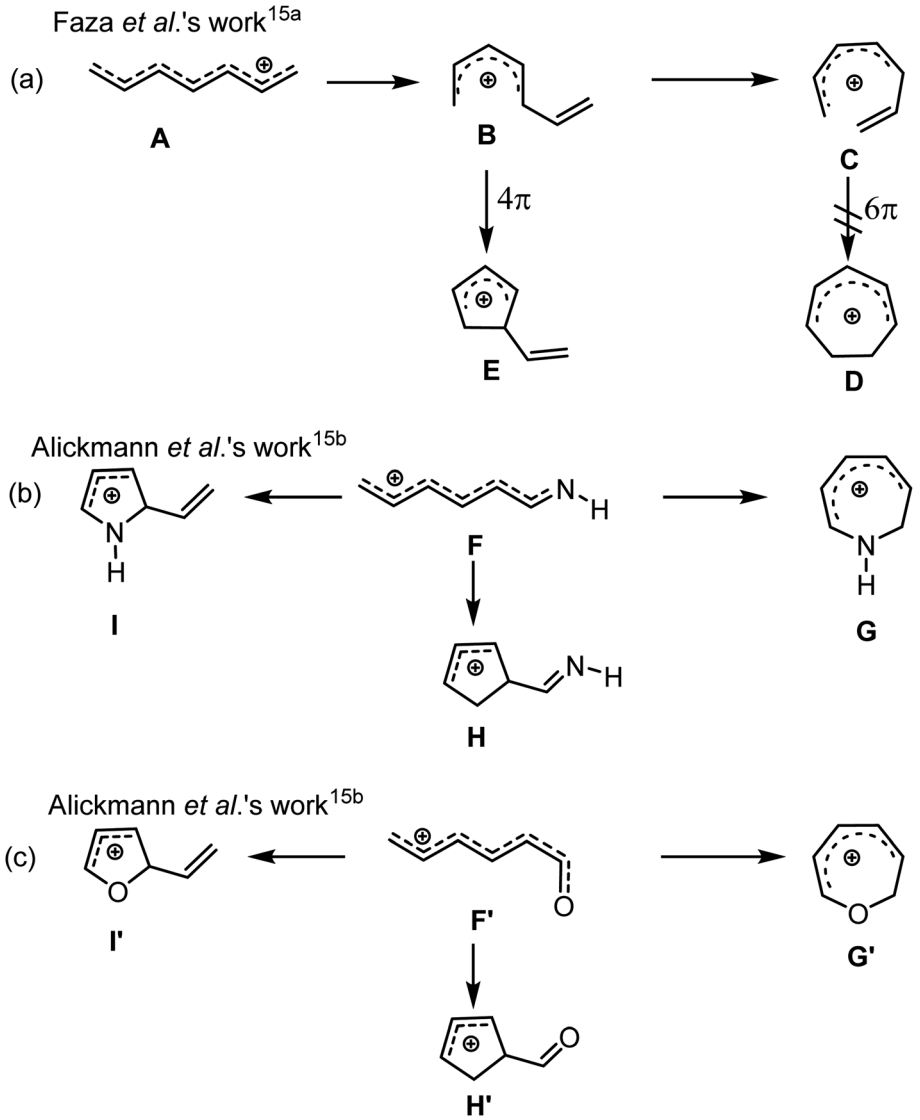
isoxazoles in an account of the reactivity of ynamides in catalytic intermolecular annulations.

Moreover, the success of the annulations between ynamides and the isoxazoles has been attributed to the key α-imino gold carbene intermediates from which various regio-, chemo- and stereo-selective transformations could occur to afford diverse N-heterocyclic compounds.[6–8] For example, the [3+2] annulation of ynamides with isoxazoles reported by Ye and coworkers to produce aminopyrroles, was made possible *via* the regioselective cyclization of the generated α-imino gold carbene intermediate. Just recently, Li *et al.*[7a] documented a series of annulations involving ynamides and isoxazoles in a review of the recent progress in the gold-catalyzed annulations of ynamides with isoxazoles derivatives. The annulations were reported to proceed *via* α-imino gold carbene intermediate which in turn afforded amino-heterocycles in a regioselective manner. In addition, Zhou *et al.*[7b] provided insights into the reaction mechanism and chemoselectivity in the cycloaddition of ynamides and isoxazoles with water. It was reported that the formation of the α-imino gold carbene complex as the key intermediate is very crucial for the formation of the product.

The synthetic prowess of pericyclic reactions has enormously increased with the development of catalytic methods.[9–11] Of the known pericyclic processes, the electrocyclization of π-conjugated acyclic compounds has particularly attracted research attention because of their high level of reliability, stereo- and regiospecificity[10,11] in constructing complex cyclic and polycyclic frameworks. Worthy of note is the Nazarov cyclization of pentadienyl cations[12] and related 6π-electrocylization of trienes,[11a,13] which are gainfully applied in synthetic organic chemistry.[11–14] For instance, the electrocyclization of pentadienyl cations generally proceeds *via* a 4π electrocyclic ring closure to provide cyclopentadienyl cation.[15a] For heptatrienyl anion, they often undergoes facile 8π electrocyclization through rapid interconversions among various anion configurations to afford seven-membered motif.[16] However, the possibility of the



Scheme 1 (a) The electrocyclization of heptatrienyl cations; (b) electrocyclization of 1-azaheptatrienyl cations; (c) electrocyclization of 1-oxaheptatrienyl cations.

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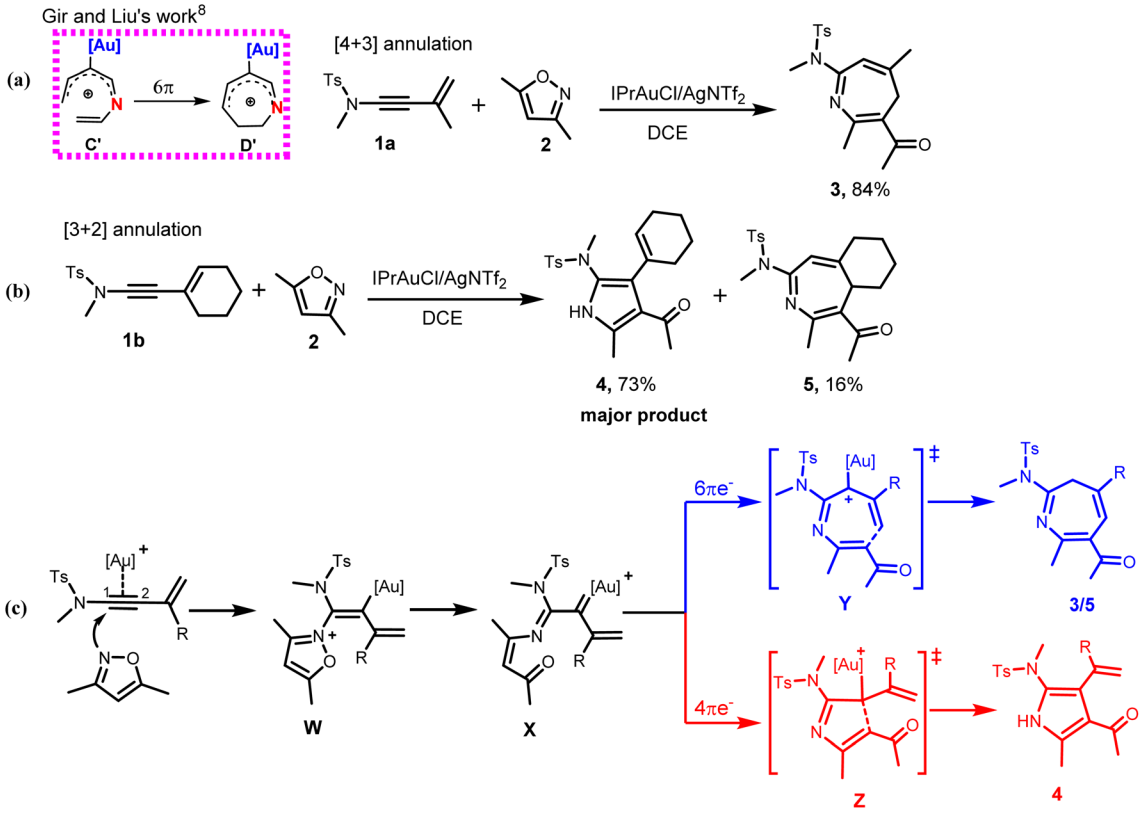
heptatrienyl cation[15,17] **A** to exclusively undergo 6π-electrocyclization through **B** to eventually generate a seven-membered motif **D** is difficult, but, cannot be ruled out (Scheme 1a, right).[15] The reason for this difficulty is due to the high energy required for **A** through **B** to form all s-cis configured cations **C** than to generate **E**.[15] Therefore, **A** exclusively undergoes typical Nazarov cyclization to afford a five-membered motif **E** (Scheme 1a, left).[15a] It has also been reported by Alickmann *et al.*[15b] that 1-aza- (Scheme 1b) and 1-oxaheptatrienyl cations (Scheme 1c) undergo various types of electrocyclizations to afford five-membered and seven-membered heterocyclic compounds, yet the path leading to the formation of **I** and **I′**, represent the kinetically preferred pathways among the pathways investigated (Scheme 1b and 1c).[15b] Moreover, Gir and Liu[8] envisaged that the incorporation of Au(I)-catalyst and nitrogen atom into **C** might circumvent the aforementioned high energy state and successfully drive the reaction of the resulting **C′** towards 6π-electrocyclization, thereby generating a seven-membered aza-cycle **D′** (Scheme 2a, left). With respect to this, they developed a particularly interesting [4+3] annulation of 3-en-1-ynamides **1a**, with 3,5-dimethylisoxazoles **2**, to exclusively produce seven-membered 4*H*-azepine product **3** (Scheme 2a, right).[8] It was also reported that when the substituent on the α-alkynyl carbon atom of the ynamide (**1a**) was replaced with a cyclohexenyl group, the annulation of the corresponding ynamide (**1b**) with **2** led to a switch in the product selectivity, majorly affording pyrrole **4** with traces of azepine product **5** (Scheme 2b).[8]

From previous studies,[5f,6–8] the mechanism of the annulation of **1a**/**1b** with **2** was postulated to involve an initial N-attack of **2** on the Au-π-alkyne complex of **1a**/**1b** to afford an iminovinyl gold intermediate **W**. This then isomerizes to the key α-imino gold(I) carbenoid **X** *via* a ring-opening process.[6–8] From this key intermediate, the unusual 6π-electron-7-atom electrocyclization could selectively take place to afford the seven-membered azepine derivatives **3**/**5** *via* the Au(I)-stabilized azaheptatrienyl cation **Y** (Scheme 2c). Alternatively, the reaction mechanism could follow the conventional reactivity of ynamides *via* 4π-electron-5-atom-electrocyclization (aza-Nazarov-type reaction) from **X**, to produce a five-membered pyrrole derivatives **4** *via* the Au(I)-stabilized pentadienyl cation **Z** (Scheme 2c).

Despite the recent advances in gold-catalyzed annulations, adequate mechanistic information is yet to be provided on how substrate modification influences the selectivity in the formation of ring systems. For instance, the successfully 6π-electrocyclization of all s-cis configured cations **C**, an isomer of heptatrienyl cation **A**, generated a seven-membered intermediate by the incorporation of Au(I)-catalyst and the nitrogen atom (Scheme 2)[8] yet, Alickmann and co-workers[15b] reported that 1-*aza*- and 1-*oxa*heptatrienyl cations would prefer the Nazarov-type cyclization to afford a five-membered heterocycle, hence the need for mechanistic clarification. Intrigued by the switch in selectivity displayed in the above annulations due to substrate modification, some puzzling questions as to which factors control the selective formation of the seven-membered product as against the five-membered



Scheme 2 The Au(I)-catalyzed annulation of ynamides with isoxazoles.

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product are yet to be answered. For example, could it be that the Au(I)-catalyst is solely responsible for the successful 6π-electrocyclization to afford the seven-membered azacycle or the cooperating effect of the Au(I)-catalyst and the nitrogen atom? Could it also be that the incorporated nitrogen atom originated from the isoxalic substrate **2** or the tosylamide group? In addition, could there be other factors responsible for the preferred selectivity besides these two factors? To answer these questions, computational studies were employed. The origin of the chemoselectivity and the factors responsible for the selective formation of **3**/**5** as against **4** in the annulation of **1a**/**1b** with **2** were unveiled. More so, the role of the incorporated Au(I)-catalyst, the nitrogen atom and the tosylamide group in facilitating the formation of the seven-membered product **3**/**5** were addressed.

Computational method

All the calculations were carried out by DFT method as implemented in the Gaussian 09 program package.[18] For the geometry optimizations of all stationary points including the transition states and intermediates, the M06 density functional method[19] was employed. For the geometry optimization, the 6-31G(d) basis set[20] was utilized for the main group atoms (N, S, O, C, H, F) while the LANL2DZ basis set[21] together with the LANL2DZ pseudopotential was employed for the Au atom. Vibrational frequency analyses at the same level of theory were performed on the optimized geometries to determine the nature of the stationary points as either minima or transition states. More so, intrinsic reaction coordinate calculations (IRC)[22] were carried out to confirm that the optimized transition states connect to their appropriate reactants and products. In order to account for solvation effects, the optimized structures in the gas phase were subjected to single-point energy (SPE) calculations at the M06/SDD[23](Au)-6-311++G(d,p)(N, S, O, C, H, F) level of theory. For these SPE calculations, the SMD solvation model as developed by Truhlar and Cramer[24] was employed, and 1,2-dichloroethane (DCE) was used as the solvent.

To account for the overestimation of entropy commonly known with DFT calculations, the translational entropy correction in solution as proposed by Whitesides *et al.*[25] was incorporated. For discussion purposes, the solvation Gibbs free energy was used. These energy values were obtained by the addition of the solvation single-point energy and the thermal correction to the Gibbs free energy. The Gibbs free energies were evaluated at 298.15 K and 1 atm. The 3D structures of some key transition states are shown using the CYLview software.[26] To reduce the computational cost, the isopropyl groups of the iPr ligand in the Au catalyst were replaced with methyl groups and the toluenesulfonyl group (Ts) were replaced with the methanesulfonyl group (Ms).

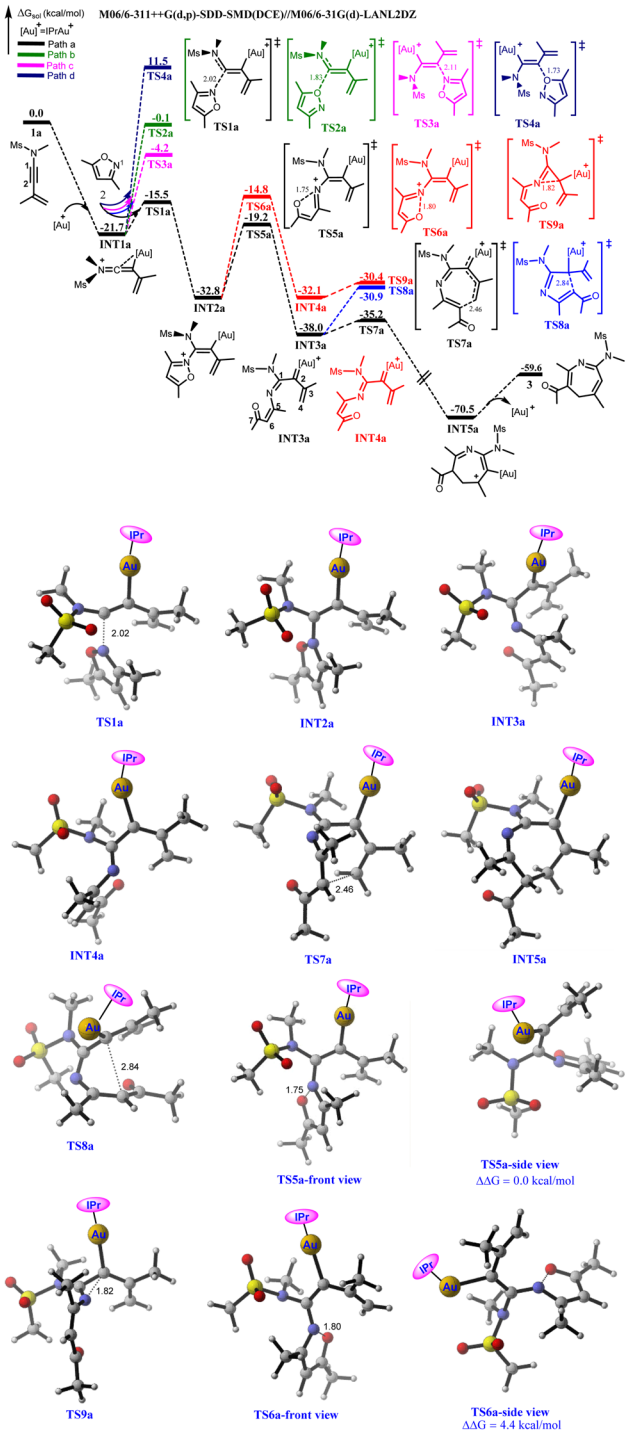

Fig. 1 Energy profile showing the gold(I)-catalyzed annulation of **1a** with **2** to afford **3**. Bond distances are given in Å.

Results and discussion

Mechanistic studies on the Au(I)-catalyzed annulation of 1a with 2 to produce 3

The annulation of **1a** with **2** commences with the coordination of the Au(I)-catalyst unto the alkyne moiety of **1a**, affording an iminovinyl intermediate (**INT1a**) in an exergonic fashion.[5f,6–8] Then, the various nucleophilic attacks of **2** on the two alkynyl carbons of **INT1a** to form vinyl gold intermediates that would eventually generate the key α-imino gold carbenoid were explored computationally. The transition state (TS) for the nucleophilic attack of the N-atom of **2** (N^1) at the C^1 of **INT1a** is optimized as **TS1a**, featuring the shortening of the $N\cdots C^1$ bond

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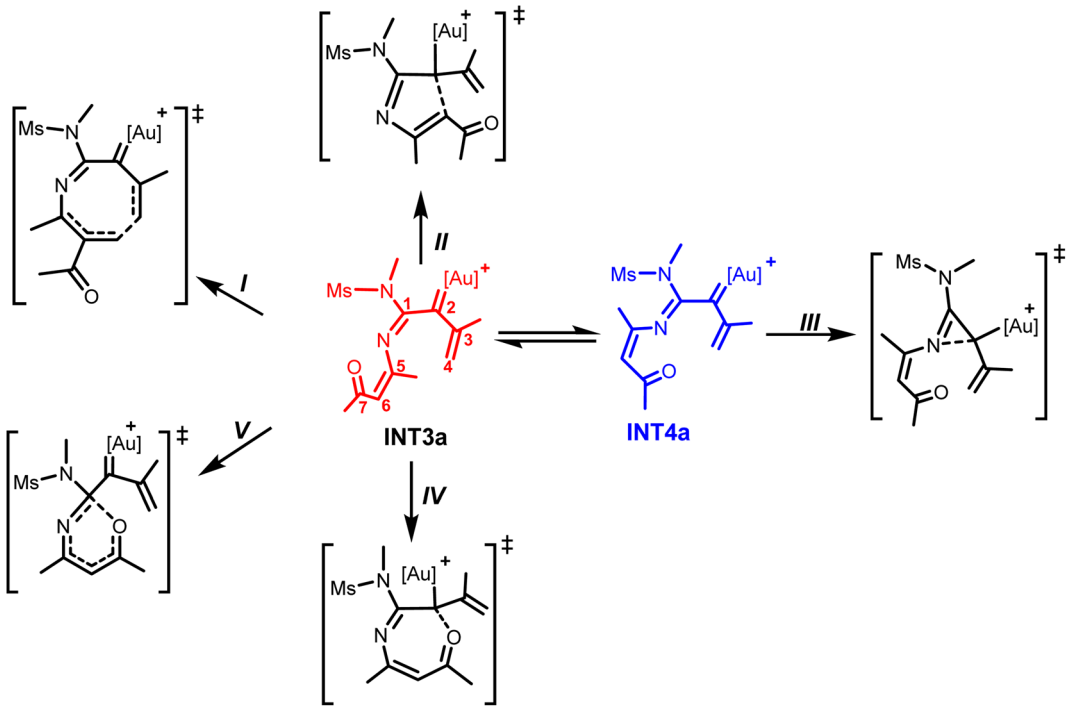
distance to 2.02 Å. The predicted energy barrier is only 6.2 kcal mol^{-1} relative to separated **INT1a** and **2** and the generated vinyl gold intermediate **INT2a** is thermodynamically stable by 11.1 kcal mol^{-1} (Path a). On the other hand, the O-atom of **2** could also compete with N^1 in attacking the C^1 of **INT1a** (Path b). For this possibility, the TS which is located as **TS2a**[27] is characterized by the O···C^1 bond distance of 1.83 Å. This nucleophilic attack requires a barrier of 21.6 kcal mol^{-1} which is substantially higher than **TS1a** by 15.4 kcal mol^{-1}, suggesting that Path "a" is more favourable than Path "b". The greater nucleophilicity of the N-atom of **2** than the O-atom could be responsible for the preferred chemoselective N-attack at the C^1 of **INT1a**.[2f] Conversely, N^1 could chemoselectively attack the C^2 of **INT1a** to generate the corresponding vinyl gold intermediate (Path c) with a (N^1···C^2) bond distance of 2.11 Å. The calculated energy barrier *via* **TS3a** is 17.5 kcal mol^{-1}, which is also significantly higher than **TS1a** by 11.3 kcal mol^{-1}. The great disparity between the energies of **TS1a** and **TS3a** could be attributed to the electron-donating ability of the N-atom of ynamides which might strongly polarize the triple bond, thus rendering C^1 more electron deficient than C^2. This greater electrophilicity of C^1 than C^2 as evident in their NPA charges (0.276e *vs.* −0.239e respectively) is beneficial for the N-nucleophilic attack of **2**. Moreover, the O-attack at C^2 of **INT1a** also represents another possibility to produce the vinyl gold complex, however, the high demanding energy barrier for this attack mode *via* **TS4a** (33.2 kcal mol^{-1} relative to separated **INT1a** and **2**) ruled out its possibility in the mechanism of the reaction (Path d). Of all the nucleophilic attack modes examined, computational results showed that the N-atom of **2** would chemo-, and regio-selectively attack C^1 of **INT1a** to produce **INT2a**, which is consistent with the experimental report (Fig. 1).[8]

Having addressed the formation of **INT2a**, the isomerization of **INT2a** to generate the key α-imino gold(I) carbenoid *via* the cleavage of the weak isoxalic N–O bond was examined next. Meanwhile, two possible structural conformers could result from the N–O bond cleavage to afford the α-imino gold(I) carbenoid. The first possible structural conformer features an increased N···O bond distance from 1.38 Å in **INT2a** to 1.75 Å in the optimized **TS5a**. With an energy barrier of 13.6 kcal mol^{-1} relative to **INT2a**, **TS5a** is expected to generate the α-imino gold carbenoid **INT3a**. The second conformer which is characterized by an N···O bond distance of 1.80 Å, has its TS located as **TS6a**. The predicted energy barrier to yield the corresponding α-imino gold(I) carbenoid **INT4a** is 18.0 kcal mol^{-1} relative to **INT2a**, implying that **TS5a** is 4.4 kcal mol^{-1} more stable than **TS6a**. The greater stability of **TS5a** than **TS6a** could be attributed to the geometrical conformation of these TSs. Examination of **TS5a** revealed that the lone pair of electrons on N^1 is oriented towards the tosylamide nitrogen (N^2) such that the π–π stacking interaction which could bring about stability to the transition state existed between the propenyl unit and the isoxazoic fragment (Fig. 1). However, for **TS6a**, the lone pair of electrons on N^1 is inclined towards the propenyl unit and the aforementioned π–π stacking interaction is absent. The geometry orientation of **TS5a** is also advantageous for the generation of the corresponding α-imino gold(I) carbenoid as **INT3a** is thermodynamically more stable than **INT4a** by 5.9 kcal mol^{-1} (Fig. 1).

It is worth noting that the electrophilic and nucleophilic sites on the formed α-imino gold(I)carbenoid could allow various intramolecular cyclization modes to afford 3-, 5-, 6- and 7-membered heterocyclic products (Scheme 3).[6–8]



Scheme 3 Possible reaction pathways from the α-imino gold(I)carbenoids INT3a and INT4a.

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The structural conformation of **INT3a** suggests that the intramolecular 6π-electrocyclization *via* the Au(I)-stabilized azaheptatrienyl would readily take place to afford a seven-membered heterocycle (Scheme 3, path I). This electrocyclization *via* the attack of the terminal alkene carbon atom (C^4) at C^6 is localized as **TS7a** with the $C^4\cdots C^6$ bond distance shortened to 2.46 Å from 3.11 Å in **INT3a**. Interestingly, the calculated energy barrier which is only 2.8 kcal mol^{-1} relative to **INT3a** indicates that the formation of the seven-membered intermediate, **INT5a** is a very facile process.

Next, the intramolecular cyclizations *via* N-, C-, and O-attack at the carbenoid moiety (C^2) to generate various heterocycles were analyzed. For instance, the Nazarov-type cyclization which is commonly proposed to access five-membered heterocycles[6a–d] could occur *via* the intramolecular attack of C^6 at the C^2 of **INT3a** (Scheme 3, path II). Relative to **INT3a**, the optimized **TS8a** for this possibility, with a $C^2\cdots C^6$ bond distance of 2.84 Å would require a barrier of 7.1 kcal mol; an energy barrier higher than **TS7a** by 4.3 kcal mol^{-1}. This computational result implies that the formation of the seven-membered intermediate *via* the $C^4\cdots C^6$ attack is more favorable than the formation of the five-membered intermediate.

Moreover, the structural orientation of **INT4a** suggests that the intramolecular cyclization leading to the formation of a three-membered intermediate would readily take place *via* N-attack at C^2 (Scheme 3, path III). The TS for the intramolecular cyclization is located as **TS9a** with its $N^1\cdots C^2$ bond distance stabilized to 1.82 Å. Although the calculated energy barrier is only 1.7 kcal mol^{-1} relative to **INT4a**, the previous N–O bond cleavage resulting in **INT4a** is less favorable compared to that leading to **INT3a**.[28] Thus, the formation of seven-membered intermediate *via* the C^6-induced cyclization at the terminal propenyl carbon atom is more favorable than the formation of the three-membered intermediate (Fig. 1). Another possible pathway explored from **INT3a** which involves an O-atom induced intramolecular cyclization at the C^2 of **INT3a** (Scheme 3, path IV) *via* **TS10a** gave a higher energy barrier than **TS7a** by 5.7 kcal mol; suggesting that this pathway is also unlikely (the $O\cdots C^2$ attack pathway is less favourable than the $C^4\cdots C^6$ attack pathway in the formation of a seven-membered intermediate, Fig. S1†). Similarly, the possibility of constructing a six-membered heterocycle *via* a 6π-electrocyclization facilitated by O-attack at C^1 of **INT3a** along **TS11a** (Scheme 3, path V) would also require an energy barrier higher than **TS7a** by 13.3 kcal mol^{-1} (Fig. S1†). Overall, these computational results indicate an overwhelming preference for the exclusive formation of a seven-membered intermediate (**INT5a**) over other possibilities explored. Therefore the reaction of **1a** with **2** would proceed through an initial N-attack of the isoxazole at the C^1 of the iminovinyl functionality of **INT1a**, after the π-alkyne activation by the Au(I) catalyst had taken place, to subsequently produce the key α-imino Au(I)-carbenoid **INT3a** *via* the N–O bond cleavage. C^6-induced intramolecular cyclization of the Au(I)-stabilized azaheptatrienyl cation at the carbenoid carbon would follow to readily produce the seven-membered intermediate **INT5a** (Fig. 1).

Subsequently, the bis(trifluoromethane)sulfonimide ion (NTf_2 counter-ion) would act as a proton shuttle in assisting the proton transfer from C^6 of **INT5a** to C^2. The TS for the deprotonation of C^6 is optimized as **TS12a**, requiring an energy barrier of 25.6 kcal mol^{-1} relative to **INT5a**. Then, the protonation of C^2 in the resulting **INT6a** would readily occur *via* **TS13a** to produce the product complex **INT7a** with a barrier of 4.8 kcal mol^{-1} relative to **INT6a**. Finally, the dissociation of the Au(I)-catalyst and the counter-ion would release the expected 4*H*-azepine product **3**. (Fig. S2†).

Mechanistic studies on the Au(I)-catalyzed annulation of 1b with 2 to produce 4 and 5

It was experimentally reported that the annulation of **1b** with **2** would generate pyrrole **4** as the major product with traces of azepine **5**.[8] After the formed iminovinyl intermediate (**INT1b**), the aforementioned nucleophilic attacks of **2** on **INT1b** were investigated. The located **TS1b** for the N-attack of **2** at C^1 of **INT1b** having its $N\cdots C^1$ bond distance shortened to 2.01 Å, demands a barrier of 5.2 kcal mol^{-1} relative to separated **INT1b** and **2**. The resulting vinyl gold(I) intermediate **INT2b** is produced in an exergonic manner. For the competitive O-attack at C^1, the computed energy barrier *via* **TS2b**[27] is 24.6 kcal mol^{-1} relative to **INT1b** and **2**, which is substantially higher than **TS1b** by 19.4 kcal mol^{-1}. The N-and O-attack at C^2 of **INT1b** *via* **TS3b** and **TS4b** were disregarded due to their higher energy barriers than **TS1b** by 11.7 kcal mol^{-1} and 26.4 kcal mol^{-1} respectively (Fig. 2). Thus, the reaction mechanism for the annulation of **1b** with **2** would chemo-, and regio-selectively proceed *via* the N-attack of **2** at C^1 of **INT1b** to produce **INT2b**, which is in excellent agreement with that for the annulation of **1a** and **2**.

The formed vinyl gold intermediate **INT2b** will subsequently undergo $N\cdots O$ bond cleavage to generate the key α-imino gold(I) carbene intermediate. For the bond cleavage *via* **TS5b** to produce α-imino gold(I) carbene intermediate **INT3b**, the $N\cdots O$ bond distance of the TS is increased to 1.73 Å and with an energy barrier of 11.0 kcal mol^{-1} relative to **INT2b**. On the other hand, the N–O bond cleavage of **INT2b** *via* **TS6b** is characterized by an increased $N\cdots O$ bond distance of 1.98 Å. The required energy barrier for this bond cleavage to afford the α-imino gold(I) carbenoid **INT4b** is 12.6 kcal mol^{-1}, which is slightly higher than **TS5b** by 1.6 kcal mol^{-1}. However, the **INT4b** formed is less stable than **INT3b** from both the kinetic and thermodynamic standpoint (Fig. 2). This result suggests that the geometrical orientation and the π–π stacking interaction between the cyclohexenyl group and the isoxazoic fragment present in **TS5b** are more beneficial for the generation of the α-imino gold carbenoid than that in **TS6b**, a finding consistent with that for the annulation of **1a** and **2**.

Next, the previously described cyclization pathways were investigated from **INT3b**. For the 6π-electrocyclization *via* the Au(I)-stabilized azaheptatrienyl cation to afford the seven-membered heterocyclic intermediate **INT5b**, the optimized **TS7b** for the electrocyclization has its $C^4\cdots C^6$ bond distance shortened to 2.30 Å, with an energy barrier of 11.3 kcal mol^{-1} relative to **INT3b**. On the other hand, the TS for the formation of

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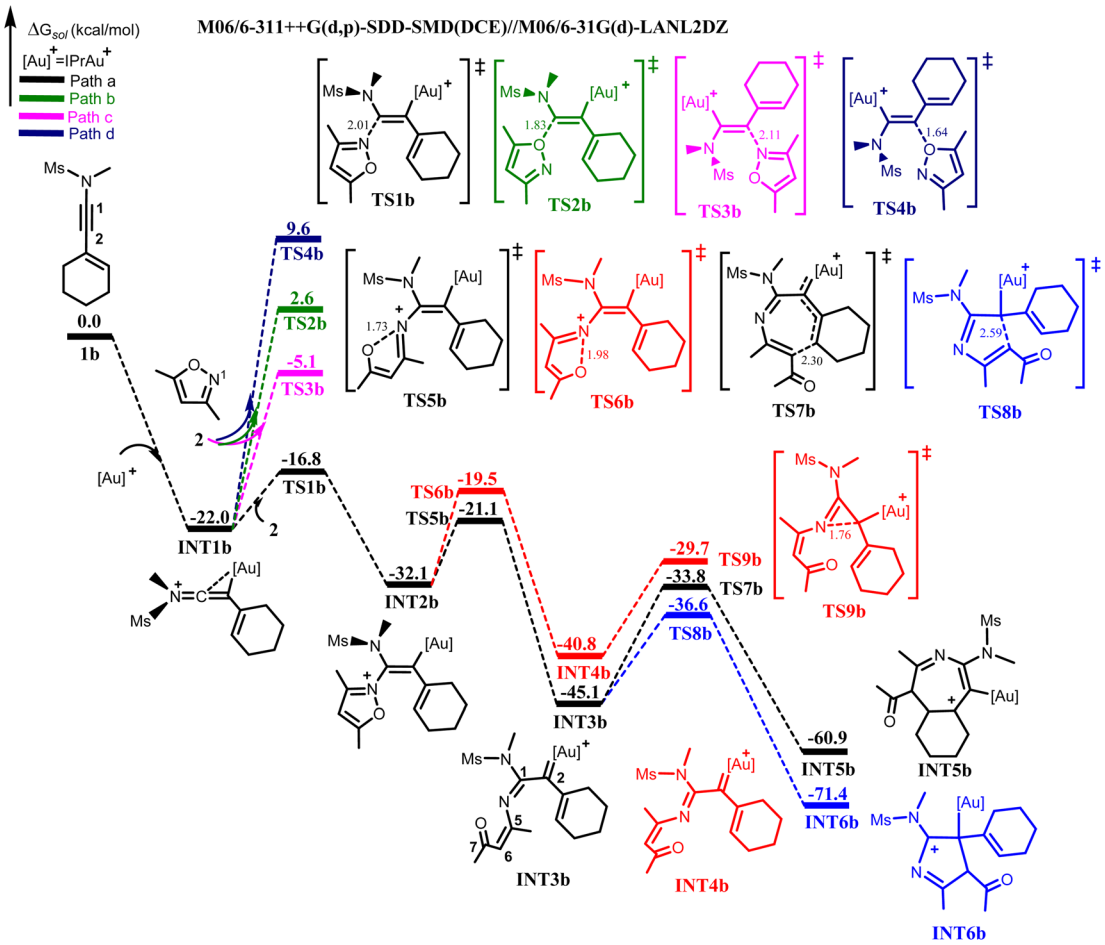

Fig. 2 Energy profile showing the gold(I)-catalyzed annulation of **1b** with **2** to generate **INT5b** and **INT6b** respectively.

the five-membered intermediate, **INT6b** is localized as **TS8b**. This intramolecular cyclization has its $C^2 \cdots C^6$ bond distance stabilized to 2.59 Å. Surprisingly, the computed energy barrier for **TS8b** is 8.5 kcal mol^{-1}, which is 2.8 kcal mol^{-1} lower than that of **TS7b**. In addition, the generated **INT6b** is also thermodynamically more stable than **INT5b** by 10.5 kcal mol^{-1}, indicating that the formation of the five-membered intermediate is more favourable than that of the seven-membered from **INT3b** (Fig. 2).

Moreover, the cyclization leading to the formation of the three-membered intermediate (**TS9b**) *via* the N-attack at C^2 of **INT4b** would require a higher energy barrier than **TS8b** by 6.9 kcal mol^{-1}. Similar to **1a**, other possible O-atom-induced intramolecular cyclization modes including the 7-, and 6-membered intramolecular cyclization were investigated from **INT3b** *via* **TS10b** and **TS11b** respectively. The results showed that the energy barriers of both transition states were higher than that of **TS8b** by 3.4 kcal mol^{-1} and 15.4 kcal mol^{-1} respectively (Fig. S3†).

With these computational results, it is therefore evident that a dramatic switch in the selectivity for the annulation of **1b** with **2** had occurred, giving preference to the formation of the five-membered intermediate over that of the seven-membered. This is against what was operational for the annulation between **1a** and **2**. It should be noted that the $\Delta\Delta G^{\ddagger}$ between **TS7b** and **TS8b** in the annulation of **1b** with **2** (2.8 kcal mol^{-1}) is smaller in comparison with that between **TS7a** and **TS8a** (4.3 kcal mol^{-1}). This suggests that the formation of the seven-membered **INT5b** cannot be completely ruled out in the annulation of **1b** with **2**. Thus, from **INT6b**, proton transfer is expected to take place to deliver the desired five-membered pyrrole product **4** as the major product, and from **INT5b**, the release of the seven-membered azepine product **5** as the side product is also expected. The computational results further validate the experimental results[8] from both kinetic and thermodynamic standpoints.

Origin of the chemo- and regio-selectivities in the annulation of the ynamides (1a/1b) with 2

It was previously stated above that clarification is needed as to why the heptatrienyl cation **A** would proceed through the high-energy intermediate **C** to generate a seven-membered heterocycle **D** by the incorporation of Au(I)-catalyst and nitrogen atom instead of the known Nazarov-type cyclization *via* **B** to produce a five-membered heterocycle **E** (Scheme 1a & 2). To address the factor(s) controlling the selective formation of the seven-membered and the five-membered product, and the role played by the incorporated Au(I) catalyst and nitrogen atom in the

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annulation of **1a**/**1b** with **2**, predictive analysis on some optimized α-imino gold(I) carbenes were carried out by computational means.

It is worth noting that Gir and Liu[8] only illustrated that the incorporation of nitrogen atom assists in the selective formation of the seven-membered azepines, however, it was not specified where the incorporated nitrogen atom originated from; whether from the isoxazole substrate **2** or the tosylamide group.

To address this, the intramolecular cyclization of the vinyl gold(I)carbenes with and without the nitrogen atom, to generate a five-membered and a seven-membered intermediate were investigated respectively to examine the role of the nitrogen atom in controlling the selectivity. The predictive analysis of the cyclization of the vinyl gold(I) carbene **A**, an intermediate having no nitrogen atom, suggests that the Nazarov-type cyclization leading to the formation of a five-membered heterocycle *via* **6a-TS** would be more favoured than the cyclization of the Au(I)-stabilized heptatrienyl motif resulting in the formation of the seven-membered heterocycle (**7a-TS**), by 13.5 kcal mol^{-1} (Schemes 4a and S1a†). When the nitrogen atom was incorporated at the position adjacent to C^1 of carbene **A**, the predictive analysis of the resulting α-imino gold(I) carbene (subsequently referred to as carbene) **B** revealed that the incorporated nitrogen atom plays no significant role in altering the selectivity; as the formation of the five-membered heterocycle *via* C^6 attack at C^2 (**6b-TS**) is still more favourable than the cyclization of the Au(I)-stabilized azaheptatrienyl cation (**7b-TS**) to form the seven-membered heterocycle, by 4.2 kcal mol^{-1} (Schemes 4a and S1a†). This finding, therefore, showed that the incorporated nitrogen atom which might stem from the isoxazole substrate is not responsible for the formation of the seven-membered azepines.

Next, the electronic effect on the substituent at C^1 of carbene **B** was examined. Carbene **C** and **D** corresponding to the methyl group and ester group as substituents at C^1 of carbene **B** were optimized respectively. The results also showed that neither the electron-donating methyl group substituent in carbene **C** nor the electron-withdrawing ester group substituent in carbene **D** alters the selectivity from the five-membered heterocycle (**6c-TS** and **6d-TS** respectively) to the seven-membered heterocycle (**7c-TS** and **7d-TS** respectively); suggesting that electronic factor at this position have no profound effect on the selectivity. Surprisingly, with the tosylamide group as a substituent at C^1 of carbene **B** to generate carbene **E** (**INT3a**), the result of the cyclization showed a switch in the product selectivity; favouring the formation of the seven-membered heterocycle *via* **TS7a** (the cyclized azaheptatrienyl cation) more than that of the five-membered (**TS8a**) by 4.3 kcal mol^{-1} (Schemes 4a and S1a†). This result clearly indicates that the tosylamide group has a profound effect on the selectivity. The reason for the observed dramatic switch in selectivity in the cyclization of carbene **E** and not in carbene **C** or **D** could be due to the interaction of the lone pair of electrons on the nitrogen atom with the π-conjugated system in carbene **E** which further stabilizes the cyclizing transition state towards 6π-electrocyclization. However such interaction was absent in carbene **C** or **D**. From these findings, it is therefore believed that the incorporated nitrogen atom reported by Gir and Liu[8] which aids the selective formation of the seven-membered azepine stemmed from the nitrogen atom of the tosylamide group.

As previously stated, the experimental report for the annulation of **1b** and **2** *via* carbene **F** (**INT3b**) majorly afforded a five-membered product.[8] The observed experimental result was validated by DFT calculations in this study (the preferred formation of the five-membered intermediate *via* **TS8b** over that of the seven-membered intermediate *via* **TS7b** by 2.8 kcal mol^{-1}). It should be noted that **1b** differs from **1a** in that the pendent propenyl group in **1a** is substituted with cyclohexenyl group in **1b**. Comparing the computational result of the cyclization of carbene **E** with that of **F**, we hypothesized that the bulkiness of the cyclohexenyl group being at the cyclization termini in carbene **F** as against the flexible pendent propenyl group in carbene **E** might allow steric hindrance during the cyclization process, hence altering the selectivity from the 6π-electrocyclization which could have afforded the seven-membered heterocycle, to the formation of the five-membered heterocycle.

To verify this hypothesis, carbene **G**, having the terminal alkenyl hydrogen atoms in carbene **E** substituted with isopropyl groups was optimized. The result of the cyclization step demonstrated that the bulkiness of the substituent indeed hindered the 6π-electrocyclization; as the formation of the five-membered heterocycle *via* **6g-TS** is more favourable than that of the seven-membered (**7g-TS**) by 11.4 kcal mol^{-1}, thus validating our hypothesis (Schemes 4b and S1b†). In support of this finding, Faza *et al.*[15a] also reported that for heptatrienyl cation having a bulky group at the cyclization termini, the 4π-electrocyclization leading to the five-membered product is more favoured than the 6π-electrocyclization leading to the seven-membered product. It can therefore be summed that the presence of the bulky cyclohexenyl group at the terminus of **1b** as against the more flexible tethered propenyl unit in **1a** causes substantial steric hindrance during the cyclization process thereby obstructing the cyclization of the azaheptatrienyl cation that could have produced the seven-membered product **5** as the major product.

Besides the steric effect being a factor in controlling the selectivity of the cyclization process of carbenes, one might wonder if the π-conjugation pattern in the carbenes can also influence such selectivity. With the predictive results of the cyclization of carbenes **E–G**, it can be presumed that the uninterrupted π-conjugation pattern in carbene **E** which is not in carbene **F** and **G** might allow the delocalization of π-electrons which stabilizes the cyclizing transition state, and such is beneficial for the 6π-electrocyclization leading to the formation of the seven-membered product. However, for carbene **F** and **G**, such extended π-conjugation pattern was interrupted, hence, the preference for the aza-Nazarov-type cyclization to afford the five-membered product. Interestingly, the experimental report documented by Gir and Liu[8] further validates our presumption. The experimental report[8] showed that when the methyl group of the propenyl unit in **1a** was replaced by a phenyl group to allow an uninterrupted π-conjugated system, the cyclization of the

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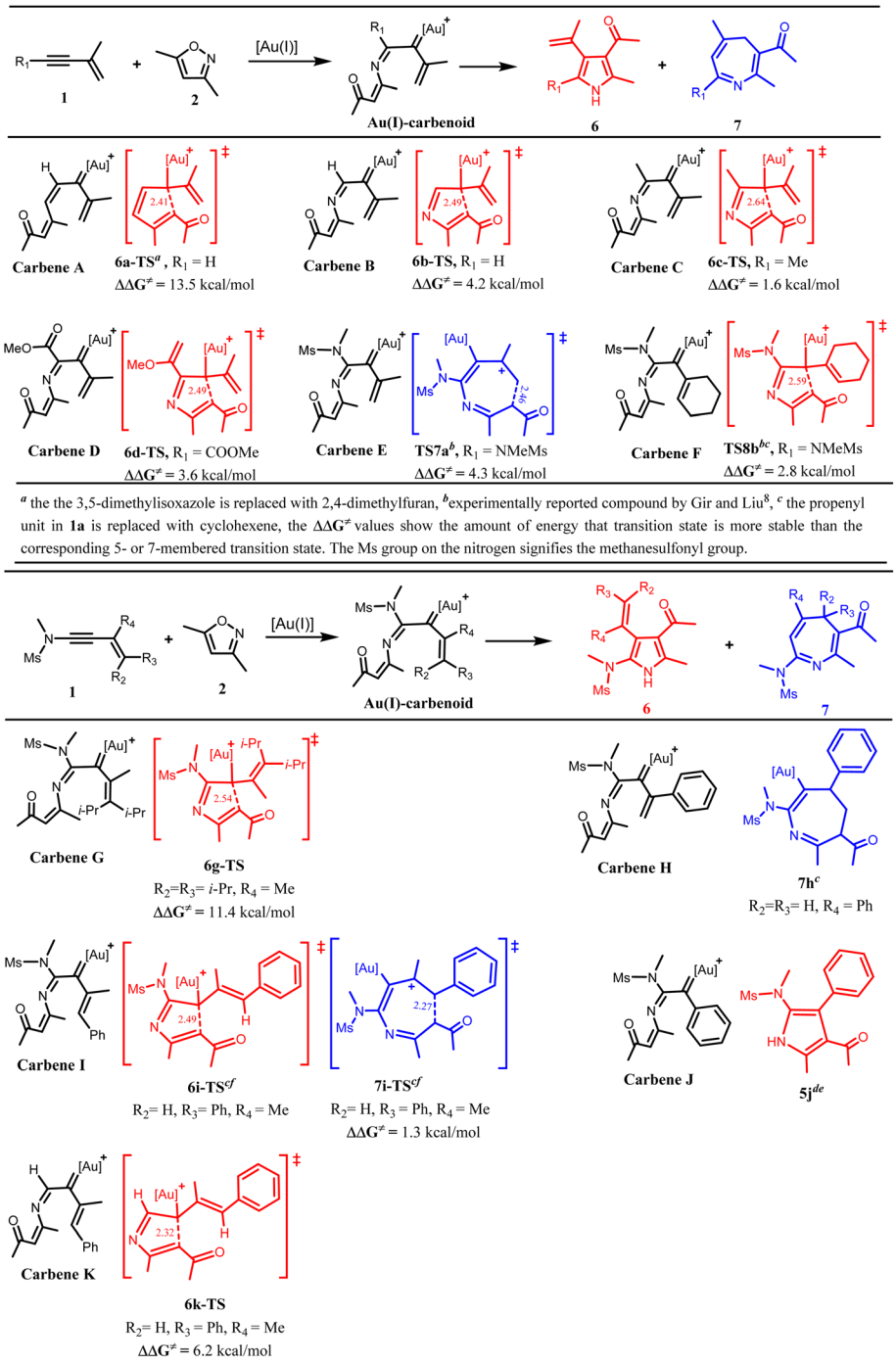
resulting carbene **H** prefers the formation of a seven-membered product (Scheme 4b).[8]

Again, the role of the conjugation pattern in controlling the selectivity was further validated in the cyclization of carbene **I**; an intermediate in which one of the terminal hydrogen atoms of the propenyl unit in carbene **E** is substituted with a phenyl group. The experimental results[8] showed that carbene **I** marginally favoured the formation of the seven-membered product with almost equal proportion with that of the five-membered product. In agreement, DFT calculations also revealed that the cyclization of carbene **I** gave a slight preference for the formation of the seven-membered heterocycle *via* **7i-TS**



Scheme 4 (a)Predictive analysis of some α-imino gold(I)-carbene intermediates. Bond distances are given in Å. (b) Predictive analysis of some α-imino gold(I)-carbene intermediates. Bond distances are given in Å.

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over that of the five-membered (**6i-TS**) by about 1.3 kcal mol^{-1}, which is consistent with the experimental findings[8] (Scheme 4b). The reason for the marginal difference in the formation of the two heterocycles was rationalized based on the competition between the aforementioned stabilizing π-orbital interaction brought about by the uninterrupted π-conjugation and the destabilizing steric hindrance caused by the presence of the bulky phenyl group at the cyclization terminus.

Meanwhile, the combined experimental and DFT studies documented by Wu and Ye's group[6a] on the cyclization of carbene **J** resulting from the Au(I) annulation of **2** with **1j** (the cyclohexenyl group in **1b** being replaced with a phenyl group to allow an uninterrupted π-conjugated system) demonstrated that carbene **J** prefers the formation of a five-membered product **5j** exclusively (Scheme 4b).[6a] This finding coupled with that on the cyclization of carbenes **E–I** clearly reveals that while the π-conjugation pattern of the carbenes influences selectivity during cyclization, the absence of steric hindrance at the cyclization terminus of the cyclizing carbenes is crucial for the exclusive formation of seven-membered products. Otherwise, the Au(I) annulation of **1** with **2** will result in the exclusive formation of five-membered products. These findings are in consonant with that reported by Faza *et al.*[15a] in the computational study on the regio-, peri-, and torquoselectivity in hydroxy heptatrienyl cation electrocyclizations.

Interestingly, the attempt to replace the tosylamide group in carbene **I** with a hydrogen atom reveals that the tosylamide group still plays a crucial role in controlling the selectivity as the cyclization of the resulting carbene **K** reverts to favouring the five-membered heterocycle over the seven-membered heterocycle (Schemes 4b and 1b). Therefore, it can be summarized that the cooperating effect of the tosylamide group on C^1, the uninterrupted π-conjugation pattern of the α-imino gold(I) carbenes and the substitution pattern at the cyclization termini to avoid steric hindrance are the key factors responsible for the different chemo-, and regio-selectivities observed in the Au(I)-catalyzed annulation of **1a**/**1b** with **2** to afford either **3**/**5** or **4**. The role of the Au(I)-catalyst is believed to assist in the stabilization of the azaheptatrienyl cation.

Conclusion

In summary, a comparative study has been carried out by DFT calculations to gain insights into the mechanisms and the origin of switchable selectivity in Au(I)-catalyzed annulations of ynamides (**1a**/**1b**) with 3,5-dimethylisoxazoles (**2**) *via* 6π-electrocyclizations of azaheptatrienyl cations. For both annulations, computational results support the overwhelming preference for the initial N-attack of the isoxazole at the electron-deficient carbon atom of the Au-π-ynamide complex to eventually form the key α-imino gold(I) carbene intermediate after N–O bond cleavage had occurred.

For the annulation of 3-en-1-ynamides (**1a**) with the **2**, the unusual 6π-electrocyclization of the Au(I)-stabilized azaheptatrienyl cations to exclusively produce a seven-membered 4*H*-azepine product **3**, after the formation of the key cationic α-imino gold(I) carbene intermediate had taken place, is preferred over the commonly proposed aza-Nazarov-type-cyclization which would afford a five-membered product. However, upon substitution of the α-alkynyl carbon atom of **1a** with a cyclohexenyl group, computational results reveal that the annulation of the corresponding ynamide **1b** with the isoxazole leads to a dramatic switch in the product selectivity; majorly affording the five-membered pyrrole **4** as the predominant product over the seven-membered azepine product **5**. The reason for the selective formation of the seven-membered azepine in the annulation of **1a** and **2** was not due to the incorporated Au(I) catalyst nor the nitrogen atom in the azaheptatrienyl cation, however, the selectivity was rationalized based on the alkene substitution pattern at the cyclization termini of the ynamides; as substituent flexibility in the cyclizing step to avoid significant steric hindrance is beneficial for the 6π-electrocyclization to afford the seven-membered product. This is against the bulky substituents at the cyclizing terminus in the annulation of **1b** and **2**. More so, the uninterrupted π-conjugation pattern in the α-imino gold(I) carbene intermediate for the annulation of **1a** with **2** allows the delocalization of π-electrons which stabilizes the transition structure, hence promoting the 6π-electrocyclization to produce the seven-membered azepine over the aza-Nazarov-type cyclization which would afford the five-membered pyrrole.

Finally, the tosylamide group as a substituent on C^1 of the Au(I)-stabilized azaheptatrienyl cation was also discovered to play a crucial role in facilitating the 6π-electrocyclization process toward the formation of the seven-membered azepine product.

It is believed that the Au(I)-catalyst helps to stabilize the azaheptatrienyl cation. It is hoped that the insight gleaned from this study will contribute significantly to the success of challenging electrocyclic reactions and facilitate the development of novel annulations that involve ynamides and other nucleophiles for the synthesis of valuable polycyclic compounds.

Conflicts of interest

The authors declare no competing financial interest.

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