View Online / Journal Homepage / Table of Contents for this issue
Dynamic Article Links

Organic &
Biomolecular
Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 4417

www.rsc.org/obc

PAPER

Mechanism of the *N*-protecting group dependent annulations of 3-aryloxy alkynyl indoles under gold catalysis: a computational study†

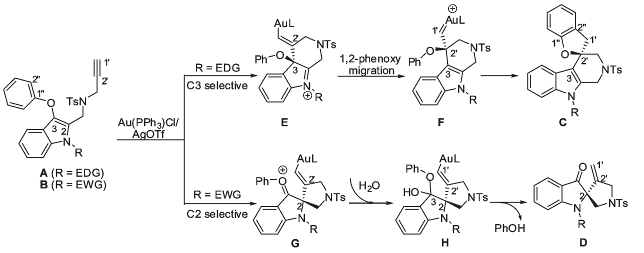
Bing Cheng, Genping Huang, Liang Xu and Yuanzhi Xia*

Received 13th February 2012, Accepted 7th April 2012
DOI: 10.1039/c2ob25316j

The mechanism of the gold-catalyzed annulations of 3-aryloxy alkynyl indoles developed by Tu *et al.* was studied by DFT calculations. It was found that both indole derivatives of electron-donating and electron-withdrawing protective groups would first undergo the 5-*exo*-dig cyclization simultaneously upon activation by cationic [PR_3Au^+] species. However, divergent reactivity of the resulting spirocyclic intermediate in competitive 1,2-alkenyl migration and nucleophilic water addition reactions towards C3 was predicted. When protected by electron-donating group, the 1,2-alkenyl migration occurs to generate a tricyclic intermediate, from which an aromatic Claisen rearrangement/nucleophilic addition sequence results in the observed 1,2-phenoxy migration. In case of electron-withdrawing group, the 1,2-alkenyl migration would be unfavorable. Instead, the nucleophilic addition of water oxygen to C3 is more facile, and leads to the hemiketal intermediate. The possible roles of water-cluster and OTf anion as proton shuttles in both reactions were also evaluated.

Introduction

The synthesis of carbocycles and heterocycles has been extensively studied, as these structural motifs are broadly represented in pharmaceuticals and natural products,[1] they are also frequently used as subunits in material sciences.[2] Homogenous gold catalysis has emerged as a powerful tool in organic synthesis in the past decade.[3] This strategy is particularly useful for the construction of ring systems, *via* the addition of an intramolecular nucleophile to the gold-activated unsaturated moiety,[4] and the reactivities of carbon,[5] oxygen,[6] nitrogen,[7] and other nucleophiles,[8] towards the gold-activated C–C triple or double bond have been well documented.



Scheme 1 Divergent annulation of alkynyl indoles and plausible mechanisms.

In this context, recent works from the Tu group disclosed interesting annulations of 3-phenoxy alkynyl indoles (**A** and **B**) under gold catalysis (Scheme 1).[9,10] They found that the synthesis of structurally interesting indole derivatives tetrahydro-β-carboline (THBC, **C**)[11] and spiro-pseudoindoxyl (**D**)[12] could be well controlled by the protective group on the indoles. According to Scheme 1, the electron-donating group-protected indole **A** may first undergo 6-*exo*-dig cyclization *via* the C3-site to give intermediate **E**, which will lead to product **C** *via* a rare 1,2-phenoxy group migration step and a Friedel–Crafts alkylation. Alternatively, the nucleophilic addition of electron-withdrawing group protected indole **B** should be more favorable at the C2-site to give a spirocyclic intermediate **G**, then the trapping of the oxacarbonium moiety at C3 of **G** by water in the reaction system furnishes hemiketal intermediate **H**. Product **D** will be formed by further phenol elimination and protodemetalation steps.

This newly developed method provides a useful synthetic protocol for natural products with related structures, and also raises interesting mechanistic questions about the controlling effect of the protective group during the nucleophilic ring-closure process, details of the unusual 1,2-phenoxy group migration, and the water effect in the reaction system.[13,14] To gain in depth understanding of the experimental observations, mechanisms of the above mentioned reactions were studied by DFT/B3LYP calculations in the current manuscript,[15] and insights into the divergent reactivity of indole derivatives of different *N*-protecting

---

College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou 325035, P.R. China. E-mail: xyz@wzu.edu.cn; Fax: +86-577-86689300

† Electronic supplementary information (ESI) available: Other possible reaction pathways, calculated geometries, energies, and Cartesian coordinates. See DOI: 10.1039/c2ob25316j

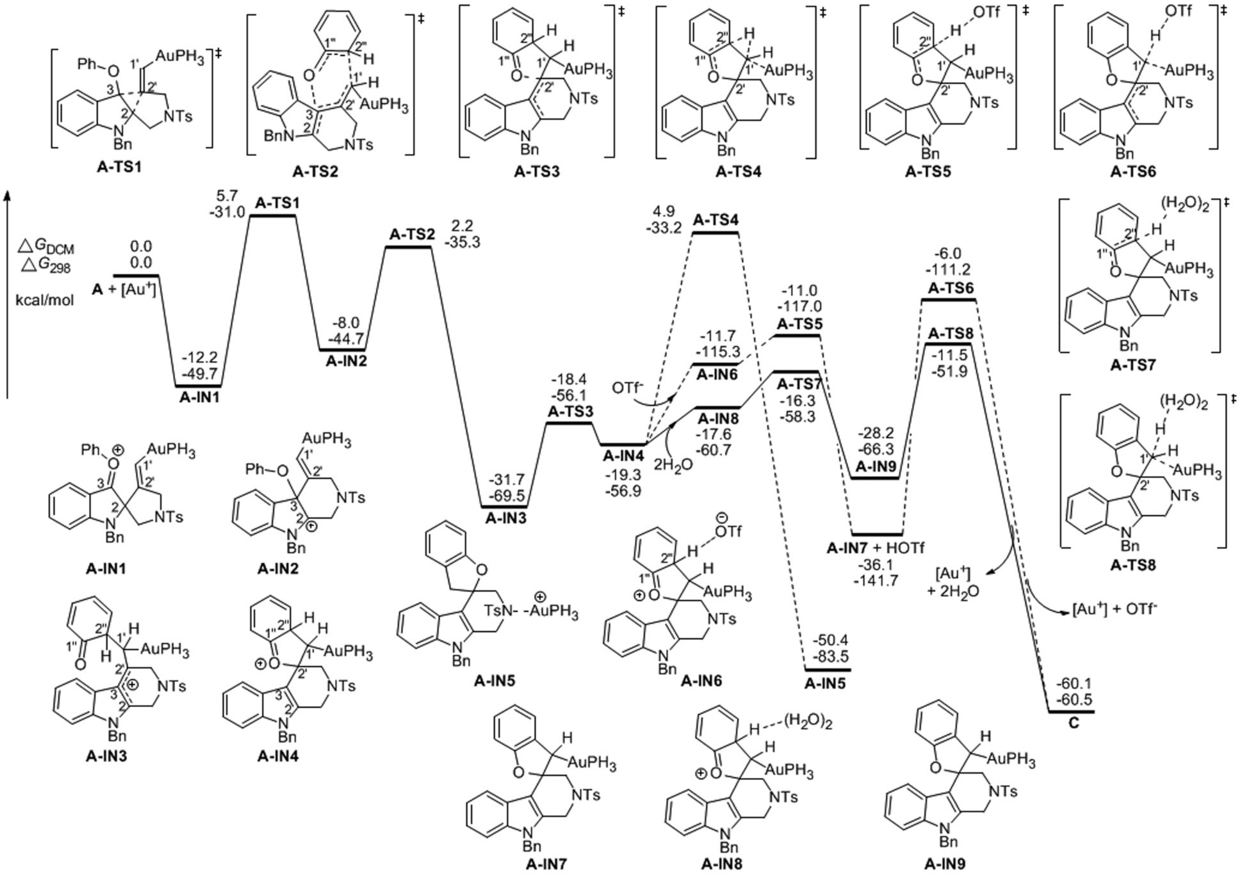


Fig. 1 Energy profile for the reaction of *N*-benzyl indole derivative **A** ([Au$^+$] = AuPH$_3$).

groups as well as details of the whole catalytic cycles are provided.

Results and discussion

Mechanism for the reaction of *N*-benzyl protected indole A

First, the potential energy surface for the reaction of substrate **A** is presented in Fig. 1, in which the indole is protected by an electron-donating benzyl group, and structures for selected transition states are given in Fig. 2. The cationic [PR$_3$Au$^+$] ([Au$^+$] in Fig. 1) is regarded as the catalytically active species in reactions, with Au(PR$_3$)Cl/AgOTf as the precatalytic system.[16] Fig. 1 shows that coordination of the alkynyl moiety of **A** to [Au$^+$] would lead to the spirocyclic intermediate **A-IN1** simultaneously from nucleophilic addition of C2 to the internal carbon of the alkyne. This process is exergonic by 12.2 kcal mol^{-1} in dichloromethane solution. The **A-IN1** could be transformed into a tricyclic intermediate **A-IN2** *via* 1,2-migration of the alkenyl moiety through **A-TS1**, in which the C2′–C2 and C2′–C3 distances are 1.905 and 1.908 Å (numbering of the atoms are given in the schemes and figures), respectively, with an activation free energy barrier of 17.9 kcal mol^{-1}. We failed to locate a transition state leading directly to **A-IN2** from a C3-site annulation. This indicates the proposed C3-annulation intermediate actually results from the ring-expansion of the C2-annulation intermediate. Instead of undergoing the proposed 1,2-phenoxy migration/Friedel–Crafts alkylation sequence to form the benzo[*b*]dihydrofuran subunit,[17] the [3,3]-sigmatropic rearrangement of **A-IN2** *via* **A-TS2** requires an activation barrier of only 10.2 kcal mol^{-1}.[18] The O–C3 and C2″–C2′ distances in this aromatic Claisen rearrangement step are 2.532 and 2.574 Å, respectively. By this route the C3–O$_{\text{Phenoxy}}$ bond is cleaved and the phenoxy moiety is transformed into the cyclohexa-2,4-dienone subunit, and intermediate **A-IN3** is formed irreversibly with a relative free energy of 31.7 kcal mol^{-1} below separated **A** and [Au$^+$]. In the following step, the nucleophilic addition of the carbonyl oxygen to C2′ *via* **A-TS3** forms spirocyclic intermediate **A-IN4**, which requires a barrier of 13.3 kcal mol^{-1} and is endergonic by 12.4 kcal mol^{-1}. Although the rearomatization of carbonyl intermediate **A-IN3** into a phenol derivative is possible,[19] the direct 1,3-H migration for such keto–enol tautomerism is energy demanding.[20] The concerted water-catalyzed tautomerization requires an activation barrier of 35.6 kcal mol^{-1} from **A-IN3**, and the activation barriers for water-cluster- or OTf anion-catalyzed deprotonation of C2″ are 20.6 and 26.0 kcal mol^{-1}, respectively.[17] Thus, the existence of a phenol intermediate from **A-IN3** was ruled out.

A last protodemetalation step from **A-IN4** will furnish the THBC product. Calculations indicate the direct 1,2-H shift *via* **A-TS4** is very energy demanding as the activation energy is as high as 36.6 kcal mol^{-1} from **A-IN3**. In light of the previous

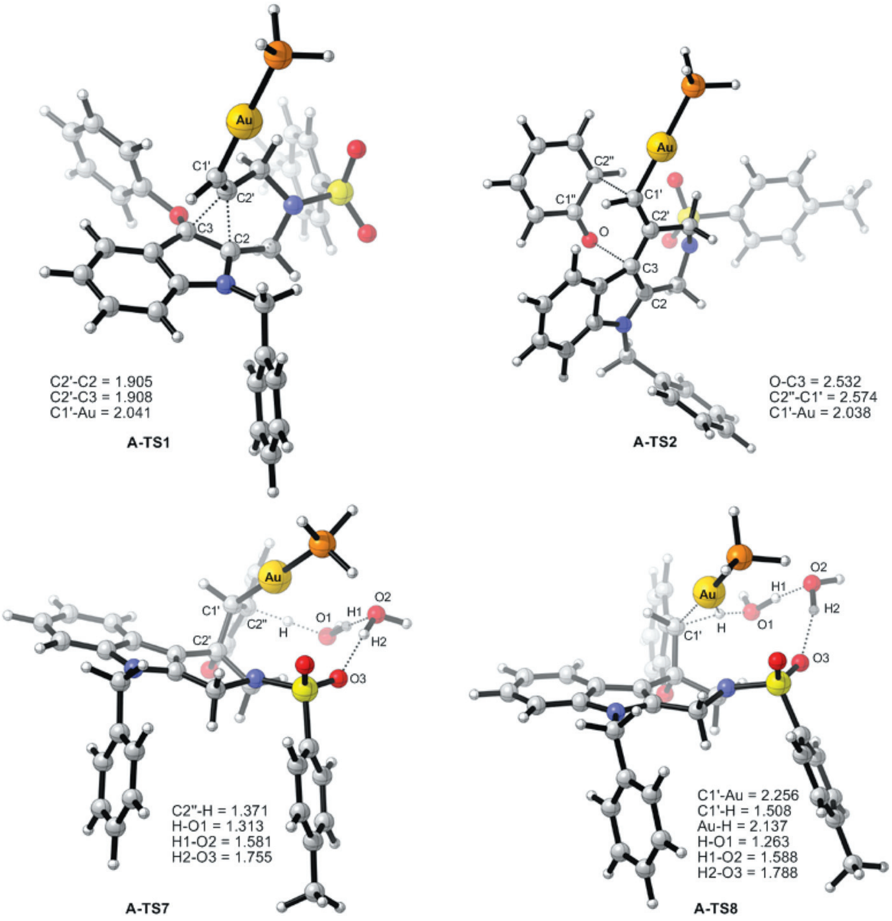
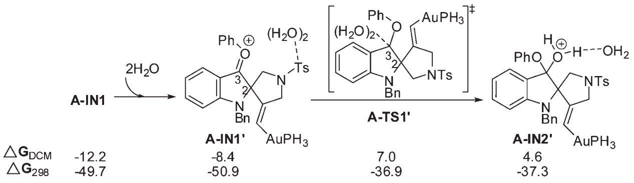


Fig. 2 Geometries for selected transition states in the reaction of substrate **A**, distances are Å.

findings of Ujaque, Yu, and others that the OTf anion[21] and water[13] may play important roles as proton shuttles in gold catalysis, we calculated the possible OTf anion and water-catalyzed H-migrations of **A-IN4**. Fig. 1 shows that the energies of the stepwise deprotonation and protonation in both cases are lower than the direct 1,2-H shift transition state **A-TS4**, and the catalysis of a two-water cluster is more efficient than that of the OTf. When OTf is involved, the coordination of OTf to **A-IN4** forms **A-IN6**, and from this complex the hydrogen on C2″ is abstracted by OTf *via* **A-TS5**, leading to **A-IN7** with the concurrent formation of HOTf exergonically. Then the protonation of C1′ by HOTf proceeds *via* **A-TS6**, which has a relative energy of 30.1 kcal mol^{-1} above **A-IN7** and HOTf, implying limited ability of the OTf anion to act as a proton shuttle in the current system.

In the water-catalyzed H-migrations, incorporation of two water molecules was found to be the most favorable.[13a,17] In this process, H-bonding complex **A-IN8** is first formed from **A-IN4** and two molecules of water. Then the deprotonation of C2″ occurs *via* **A-TS7**, leading endergonically to intermediate **A-IN9** with a small barrier of 1.3 kcal mol^{-1}. The protonation of C1′ is completed *via* **A-TS8**, which is 20.2 kcal mol^{-1} above the relative energy of **A-IN3**. The protodemetalation *via* **A-TS8** has the highest activation barrier in the potential energy surface, thus limiting the rate of the annulation of indole **A**. The geometries of **A-TS7** and **A-TS8** (Fig. 2) show strong H-bonding networks between the water molecules and between water and the carbonyl oxygen of the Ts moiety, making the H-migrations catalyzed by a two-water cluster the most favorable.



Scheme 2 Possible addition of water to **A-IN1**.

The above results show the formation of THBC derivative **C** from **A** starts with a barrierless 5-*exo*-dig cyclization to generate spirocyclic intermediate **A-IN1**. According to Tu *et al.*,[9] this type of species is the key intermediate in the reaction of **B**, which could be quenched by water in the system and is transformed into a pseudoindoxyl intermediate by lost a molecule of phenol. Thus, the possible reaction between **A-IN1** and water is estimated. Theoretically, the nucleophilic addition of water to C3 may be realized by one water or water clusters.[13a] Calculations indicate the involvement of two molecules of water is the most favorable,[17] which is shown in Scheme 2. The formation of H-bonding complex **A-IN1′** is slightly endergonic by 3.8 kcal

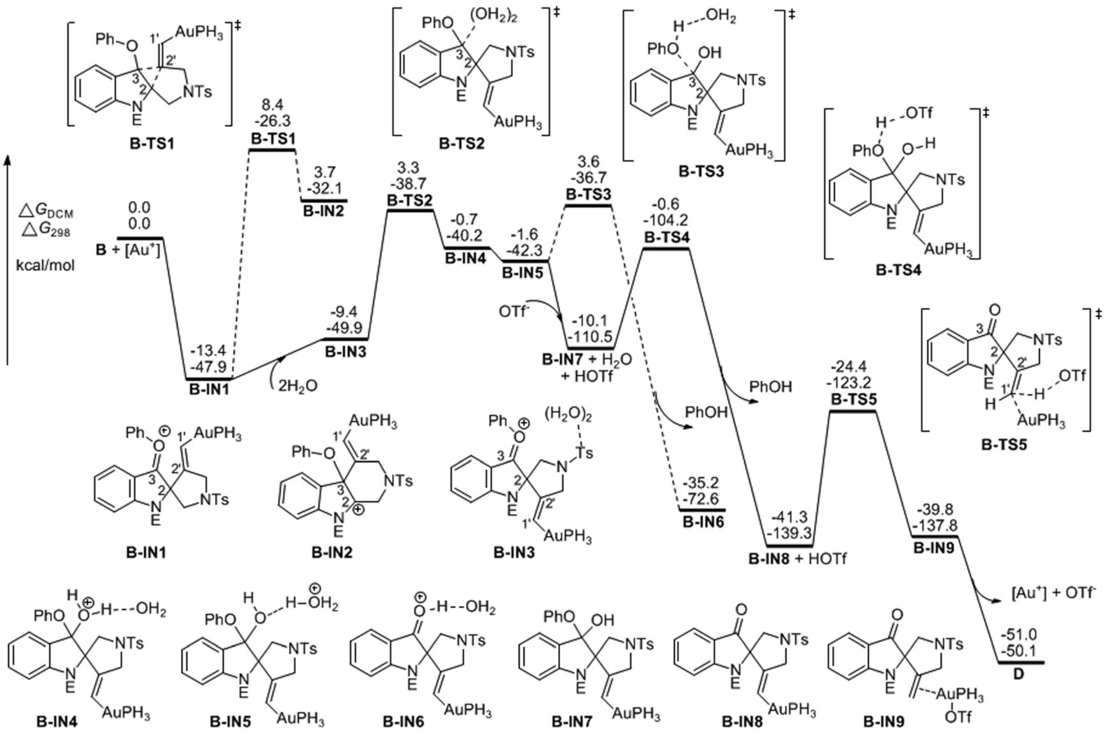


Fig. 3 Energy profile for the reaction of *N*–CO_2Me indole derivative **B** ($[Au^+] = AuPH_3$).

mol^{-1}. Then the nucleophilic addition of the oxygen of one water molecule to C3 proceeds *via* **A-TS1**, with an activation barrier of 19.2 kcal mol^{-1}. However, in comparison with the 1,2-alkenyl migration *via* **A-TS1**, this nucleophilic addition step is 1.3 kcal mol^{-1} higher in activation energy, and the generated intermediate **A-IN2′** is 12.6 kcal mol^{-1} higher in energy than **A-IN2**, indicating the quenching of the C2 annulation intermediate of benzyl protected indole **A** by water is unfavorable both kinetically and thermodynamically. Thus, the water-cluster may act as a proton shuttle in the **A** system, but no trapping of the cationic intermediate **A-IN1** occurs, and only the THBC derivative **C** could be observed as a result of the irreversible 1,2-alkenyl migration.

Mechanism for the reaction of *N*–CO_2Me protected indole B

We next discuss the mechanism for the formation of spiro-pseudoindoxyl derivative from *N*–CO_2Me protected indole precursor **B**, with the potential energy surface given in Fig. 3 and the geometric structures for selected intermediates and transition states depicted in Fig. 4. The initiation of the reaction is similar to that given in Fig. 2, that the 5-*exo*-dig cyclization of substrate **B** into spirocyclic intermediate **B-IN1** is a barrierless process upon the coordination of the alkynyl moiety to $[Au^+]$. Then from **B-IN1**, two types of reaction, the 1,2-alkenyl migration from C2 to C3 (**B-TS1**) and the nucleophilic addition of water to C3 (**B-TS2**), are possible. Fig. 3 indicates the activation energy for the former process is about 21.8 kcal mol^{-1}, being about 5.1 kcal mol^{-1} higher that of the nucleophilic water addition step. It is also found that the resulting intermediate (**B-IN2**) of the 1,2-alkenyl migration is 17.1 kcal mol^{-1} less stable as relative to **B-IN1**. This outcome should be attributed to the fact that the positive charge populated on C2 of intermediate **B-IN2** could not be well stabilized by the neighboring nitrogen atom, which is substituted by an electron-withdrawing CO_2Me group. Actually, the *N*–Bn containing intermediate **A-IN2** is only 4.2 kcal mol^{-1} higher in energy than **A-IN1**, demonstrating the dramatic influence of the protective group on the stability of the 1,2-alkenyl migration intermediate. Geometric structure shows the **B-TS1** resembles more to **B-IN2** with the C2′–C2 and C2′–C3 distances being 1.893 and 1.786 Å, respectively, thus higher activation barrier is required, as predicted by the Hammond postulate.[23] The 5.1 kcal mol^{-1} energy difference between **B-TS1** and **B-TS2** is in good agreement with the experimental observations,[9] that only the spiro-pseudoindoxyl product **D** from the water addition and further transformations was obtained in the reaction of indole **B**.

In the nucleophilic water addition process, the lowest activation energy pathway requires two water molecules,[17] which could form H-bonding networks for stabilization of the positive charges. First of all, complex **B-IN3** is formed from **B-IN1** and two water molecules with the free energy increased by 4.0 kcal mol^{-1}. Then the nucleophilic attack of oxygen of one water to C3 is completed *via* **B-TS2** with the O1–C3 distance being 1.878 Å. This step leads endergonically to intermediate **B-IN4**, in which the positive charge on O1 is stabilized by the other water molecule by forming O2···H1–O1 hydrogen bonding with the O2–H1 and H1–O1 distances being 1.376 and 1.101 Å, respectively. **B-IN4** could isomerize to the slightly more stable cation **B-IN5** by transferring the proton H1 to O2, changing the O2–H1 and H1–O1 distances to 1.046 and 1.516 Å, respectively.

After the water addition, the reaction would undergo phenol elimination step to generate the C3 ketone moiety. Calculations

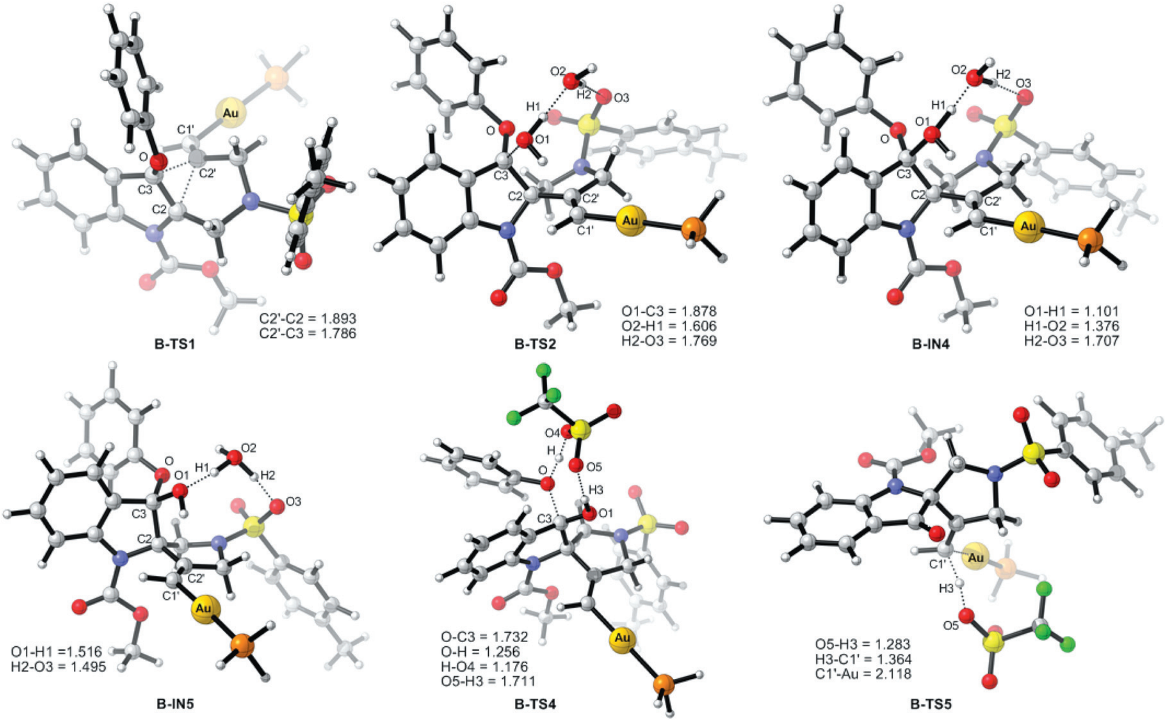


Fig. 4 Geometric structures for selected intermediates and transition states in the reaction of substrate **B**, distances are Å.

indicate the breaking of C3–O$_{\text{Phenoxy}}$ bond of **B-IN5** could be realized by passing **B-TS3** with a breaking C3–O distance of 1.772 Å. This step requires an activation barrier of only 5.2 kcal mol^{-1} from **B-IN5** and leads irreversibly to a protonated carbonyl intermediate **B-IN6** that is stabilized by the residual water.[22] However, if OTf counterion is involved, the transformation of cationic **B-IN5** into a neutral system of hemiketal **B-IN7**, H_2O, and HOTf is thermodynamically more favorable. Then the phenol elimination from **B-IN7** occurs *via* **B-TS4** with the HOTf as a proton shuttle, which donates the proton to the phenoxy group (O4$_{\text{OTf}}$–H = 1.176 and H–O$_{\text{Phenoxy}}$ = 1.256 Å) and abstracts the proton of the C3 hydroxyl group (O5$_{\text{OTf}}$–H3$_{\text{Hydroxyl}}$ = 1.711 Å) in a single step. The energy of **B-TS4** is 3.0 kcal mol^{-1} lower than **B-TS3**, thus the HOTf involved phenol elimination is more favorable. This step leads to ketone intermediate **B-IN8**, from which the final protodemetalation occurs *via* **B-TS5**. In this step the alkenyl gold moiety is protonated by HOTf (O5$_{\text{OTf}}$–H3 = 1.283, H3–C1′ = 1.364, and C1′–Au = 2.118 Å) with an activation free energy of 16.9 kcal mol^{-1}. The dissociation of π complex **B-IN9** is exergonic and product **D** is 51.0 kcal mol^{-1} lower in energy than the starting material.

Conclusions

In conclusion, the divergent annulations of alkynyl indoles under gold catalysis were studied by DFT/B3LYP calculations. The results reveal that in both reactions of indole derivatives protected by electron-donating and electron-withdrawing groups, the 5-*exo*-dig cyclization will occur simultaneously upon activation of the alkynyl moiety by cationic [PR_3Au^+]. Then different reactivity of the resulted spirocyclic intermediates was calculated. When the indole is protected by an electron-donating benzyl group, the 1,2-migration of the alkenyl moiety leads to a tricyclic intermediate, from which the cleavage of the C3–O$_{\text{Phenoxy}}$ bond occurs by an aromatic Claisen rearrangement. Then the benzo[*b*]dihydrofuran subunit is formed by addition of the carbonyl oxygen to construct an oxaquaternary carbon center. The final protodemetalation to form the spiro-THBC product is realized *via* a two-water cluster catalyzed H-migrations, and is the rate-determining step of the whole reaction. On the other hand, the spirocyclic intermediate from the 5-*exo*-dig cyclization of electron-withdrawing group protected indole substrate could be trapped more easily by a two-water cluster than the 1,2-alkenyl migration, as the positive charge on C2 of the resulted intermediate from the latter step could not be well stabilized in this case. After the addition of water to C3, the hemiketal intermediate is formed with the OTf counterion involved as a proton acceptor. The generated HOTf could participate in the following phenol elimination step as a proton shuttle, and it is also the hydrogen donor for the final protodemetalation of the alkenyl gold moiety. These results provide mechanistic insights for the experimental observations of Tu *et al.*,[9] and should have application in the future design of new reactions.

Computational section

All of the calculations were carried out with the Gaussian 09[24] computational program suite. All stationary points along the reaction coordinate were fully optimized at the DFT level using B3LYP hybrid functional.[25] The standard 6-31G* basis set[26] was applied for all the atoms except Au, which was described by the LANL2DZ basis set.[27] Frequencies were analytically computed at the same level of theory to obtain the gas phase free energies and to confirm whether the structures are minima (no imaginary frequency) or transition states (only one imaginary frequency). Intrinsic reaction coordinate (IRC) calculations[28] were carried out to conform that all transition state structures connect the proposed reactants and products. The solvation effect was examined by performing single-point self-consistent reaction field (SCRF) calculations based on the polarizable continuum model (PCM) for gas-phase optimized structures. Dichloromethane (DCM, ε = 8.9) were used as the solvent, corresponding to the experimental conditions. Solvation free energies (ΔG_{DCM}) were calculated by adding the solvation energies to the computed gas phase relative free energies (ΔG_{298}). Unless stated otherwise, all the energies in the results and discussion section are the solvation-corrected free energies, and all the energies are relative to energy sum of [PH_3Au^+] and the corresponding indole precursor.

Acknowledgements

This work is financially supported by the National Natural Science Foundation of China (Grant No. 21002073), Wenzhou Science & Technology Bureau (Grant No. Y20100003), and Wenzhou University (Startup funding to Y.X.). B.C. is supported by the Xinmiao Talent Program of Zhejiang Province (No. 2010R424044). All computations were done on the High Performance Computation Platform of Wenzhou University.

Notes and references

1 For selected reviews, see: (*a*) S. M. Abu Sohel and R.-S. Liu, *Chem. Soc. Rev.*, 2009, **38**, 2269; (*b*) K. C. Majumdar, P. Debnath and B. Roy, *Heterocycles*, 2009, **78**, 2661; (*c*) N. T. Patil and Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3395; (*d*) V. Michelet, P. Y. Toullec and J.-P. Genêt, *Angew. Chem., Int. Ed.*, 2008, **47**, 4268; (*e*) S. F. Kirsch, *Synthesis*, 2008, 3183; (*f*) M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952; (*g*) T. J. Donohoe, A. J. Orr and M. Bingham, *Angew. Chem., Int. Ed.*, 2006, **45**, 2664; (*h*) C. Bruneau, *Angew. Chem., Int. Ed.*, 2005, **44**, 2328; (*i*) F. Alonso, I. P. Beletskaya and M. Yus, *Chem. Rev.*, 2004, **104**, 3079; (*j*) I. Nakamura and Y. Yamamoto, *Chem. Rev.*, 2004, **104**, 2127; (*k*) G. C. Lloyd-Jones, *Org. Biomol. Chem.*, 2003, **1**, 215; (*l*) C. Aubert, O. Buisine and M. Malacria, *Chem. Rev.*, 2002, **102**, 813; (*m*) B. M. Trost, F. D. Toste and A. B. Pinkerton, *Chem. Rev.*, 2001, **101**, 2067.

2 For selected reviews, see: (*a*) H. Fan, J. Peng, M. T. Hamann and J.-F. Hu, *Chem. Rev.*, 2008, **108**, 264; (*b*) C. J. Morris and A. J. Phillips, *Nat. Prod. Rep.*, 2008, **25**, 95; (*c*) J. W. Huffman and L. W. Padgett, *Curr. Med. Chem.*, 2005, **12**, 1395; (*d*) C. Bailly, *Curr. Med. Chem.: Anti-Cancer Agents*, 2004, **4**, 363; (*e*) N. J. L. Guernion and W. Hayes, *Curr. Org. Chem.*, 2004, **8**, 637; (*f*) A. Fürstner, *Angew. Chem., Int. Ed.*, 2003, **42**, 3582; (*g*) H. Hoffmann and T. Lindel, *Synthesis*, 2003, 1753; (*h*) J. O. Jeppesen and J. Becher, *Eur. J. Org. Chem.*, 2003, 3245; (*i*) M. Kidwai, R. Venkataramanan, R. Mohan and P. Sapra, *Curr. Med. Chem.*, 2002, **9**, 1209; (*j*) J. W. Huffman, *Curr. Med. Chem.*, 1999, **6**, 705; (*k*) D. Curran, J. Grimshaw and S. D. Perera, *Chem. Soc. Rev.*, 1991, **20**, 391.

3 For reviews: (*a*) A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2010, **49**, 5232; (*b*) A. Das, S. M. Abu Sohel and R.-S. Liu, *Org. Biomol. Chem.*, 2010, **8**, 960; (*c*) A. Fürstner, *Chem. Soc. Rev.*, 2009, **38**, 3208; (*d*) P. Belmont and E. Parker, *Eur. J. Org. Chem.*, 2009, 6075; (*e*) D. J. Gorin, B. D. Sherry and F. D. Toste, *Chem. Rev.*, 2008, **108**, 3351; (*f*) R. A. Widenhoefer, *Chem.–Eur. J.*, 2008, **14**, 5382; (*g*) Z. Li, C. Brouwer and C. He, *Chem. Rev.*, 2008, **108**, 3239; (*h*) A. Arcadi, *Chem. Rev.*, 2008, **108**, 3266; (*i*) B. Crone and S. F. Kirsch, *Chem.–Eur. J.*, 2008, **14**, 3514; (*j*) H. C. Shen, *Tetrahedron*, 2008, **64**, 3885; (*k*) H. C. Shen, *Tetrahedron*, 2008, **64**, 7847; (*l*) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Commun.*, 2007, 333; (*m*) D. J. Gorin and F. D. Toste, *Nature*, 2007, **446**, 395; (*n*) A. Fürstner and P. W. Davies, *Angew. Chem., Int. Ed.*, 2007, **46**, 3410; (*o*) A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180; (*p*) L. Zhang, J. Sun and S. A. Kozmin, *Adv. Synth. Catal.*, 2006, **348**, 2271; (*q*) A. S. K. Hashmi and G. J. Hutchings, *Angew. Chem., Int. Ed.*, 2006, **45**, 7896; (*r*) S. Ma, S. Yu and Z. Gu, *Angew. Chem., Int. Ed.*, 2006, **45**, 200; (*s*) R. Skouta and C.-J. Li, *Tetrahedron*, 2008, **64**, 4917.

4 For reviews, see: (*a*) E. Soriano and J. Marco-Contelles, *Acc. Chem. Res.*, 2009, **42**, 1026; (*b*) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Rev.*, 2008, **108**, 3326; (*c*) J. Marco-Contelles and E. Soriano, *Chem.–Eur. J.*, 2007, **13**, 1350; (*d*) A. Corma, A. Leyva-Pérez and M. J. Sabater, *Chem. Rev.*, 2011, **111**, 1657; (*e*) M. Rudolph and A. S. K. Hashmi, *Chem. Commun.*, 2011, **47**, 6536; (*f*) N. D. Shapiro and F. D. Toste, *Synlett*, 2010, **5**, 675; (*g*) A. S. K. Hashmi, *Pure Appl. Chem.*, 2010, **82**, 657.

5 (*a*) E. Soriano and J. Marco-Contelles, *Chem.–Eur. J.*, 2008, **14**, 6771; (*b*) T. Matsuda, Y. Yamaguchi, M. Shigeno, S. Sato and M. Murakami, *Chem. Commun.*, 2011, **47**, 8697; (*c*) C. Gronnier, Y. Odabachian and F. Gagosz, *Chem. Commun.*, 2011, **47**, 218; (*d*) A. S. K. Hashmi, T. Häffner, M. Rudolph and F. Rominger, *Chem.–Eur. J.*, 2011, **17**, 8195; (*e*) A. S. K. Hashmi, M. Rudolph, J. Huck, W. Frey, J. W. Bats and M. Hamzic, *Angew. Chem., Int. Ed.*, 2009, **48**, 5848.

6 (*a*) J. Renault, Z. Qian, P. Uriac and N. Gouault, *Tetrahedron Lett.*, 2011, **52**, 2476; (*b*) X. Zhang, Z. Lu, C. Fu and S. Ma, *J. Org. Chem.*, 2010, **75**, 2589; (*c*) S. Kim, D. Kang, S. Shin and P. H. Lee, *Tetrahedron Lett.*, 2010, **51**, 1899; (*d*) Y. Liu, F. Song, Z. Song, M. Liu and B. Yan, *Org. Lett.*, 2005, **7**, 5409; (*e*) X. Du, F. Song, Y. Lu, H. Chen and Y. Liu, *Tetrahedron*, 2009, **65**, 1839; (*f*) J. Zhang and H.-G. Schmalz, *Angew. Chem., Int. Ed.*, 2006, **45**, 6704; (*g*) A. Blanc, K. Tenbrink, J.-M. Weibel and P. Pale, *J. Org. Chem.*, 2009, **74**, 5342; (*h*) M. Egi, K. Azechi and S. Akai, *Org. Lett.*, 2009, **11**, 5002; (*i*) A. S. K. Hashmi, L. Schwarz, J.-H. Choi and T. M. Frost, *Angew. Chem., Int. Ed.*, 2000, **39**, 2285.

7 (*a*) S. Kramer, J. L. H. Madsen, M. Rottlander and T. Skrydstrup, *Org. Lett.*, 2010, **12**, 2758; (*b*) F. M. Istrate and F. Gagosz, *Org. Lett.*, 2007, **9**, 3181; (*c*) A. Saito, T. Konishi and Y. Hanzawa, *Org. Lett.*, 2010, **12**, 372; (*d*) Y. Lu, X. Fu, H. Chen, X. Du, X. Jia and Y. Liu, *Adv. Synth. Catal.*, 2009, **351**, 129.

8 (*a*) I. Nakamura, U. Yamagishi, D. Song, S. Konta and Y. Yamamoto, *Angew. Chem., Int. Ed.*, 2007, **46**, 2284; (*b*) I. Nakamura, T. Sato, M. Terada and Y. Yamamoto, *Org. Lett.*, 2007, **9**, 4081; (*c*) I. Nakamura, T. Sato, M. Terada and Y. Yamamoto, *Org. Lett.*, 2008, **10**, 2649.

9 Y.-Q. Zhang, D.-Y. Zhu, Z.-W. Jiao, B.-S. Li, F.-M. Zhang, Y.-Q. Tu and Z. Bi, *Org. Lett.*, 2011, **13**, 3458.

10 For recent synthesis of indole derivatives by gold catalysis, see: (*a*) W. Kong, C. Fu and S. Ma, *Chem.–Eur. J.*, 2011, **17**, 13134; (*b*) X. Xie, X. Du, Y. Chen and Y. Liu, *J. Org. Chem.*, 2011, **76**, 9157; (*c*) P. Kothandaraman, S. R. Mothe, S. S. M. Toh and P. W. H. Chan, *J. Org. Chem.*, 2011, **76**, 7633; (*d*) Y. Lu, X. Du, X. Jia and Y. Liu, *Adv. Synth. Catal.*, 2009, **351**, 1517; (*e*) G. Li and Y. Liu, *J. Org. Chem.*, 2010, **75**, 3526; (*f*) Y. Liu, W. Xu and X. Wang, *Org. Lett.*, 2010, **12**, 1448; (*g*) G. Verniest, D. England, N. D. Kimpe and A. Padawa, *Tetrahedron*, 2010, **66**, 1496; (*h*) J. Barluenga, A. Fernandez, F. Rodriguez and J. Fananas, *J. Organomet. Chem.*, 2009, **694**, 546; (*i*) C. Ferrer, A. Escribano-Cuesta and A. M. Echavarren, *Tetrahedron*, 2009, **65**, 9015; (*j*) D. B. England and A. Padwa, *Org. Lett.*, 2008, **10**, 3631; (*k*) G. Zhang, X. Huang, G. Li and L. Zhang, *J. Am. Chem. Soc.*, 2008, **130**, 1814; (*l*) T. Yang, L. Campbell and D. J. Dixon, *J. Am. Chem. Soc.*, 2007, **129**, 12070; (*m*) C. Liu and R. A. Widenhoefer, *Org. Lett.*, 2007, **9**, 1935; (*n*) C. Ferrer, C. H. M. Amijs and A. M. Echavarren, *Chem.–Eur. J.*, 2007, **13**, 1358; (*o*) C. Ferrer and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2006, **45**, 1105; (*p*) L. Zhang, *J. Am. Chem. Soc.*, 2005, **127**, 16804; (*q*) Z. Li, Z. Shi and C. He, *J. Organomet. Chem.*, 2005, **690**, 5049.

11 (*a*) T. Raheem, P. S. Thiara, E. A. Peterson and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2007, **129**, 13404; (*b*) J. Seayad, A. M. Seayad and B. List, *J. Am. Chem. Soc.*, 2006, **128**, 1086; (*c*) T. Ulven and E. Kostenis, *J. Med. Chem.*, 2005, **48**, 897; (*d*) M. S. Taylor and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2004, **126**, 10558; (*e*) X. Li, L. Zhang, W. Zhang, S. E. Hall and J. P. Tam, *Org. Lett.*, 2000, **2**, 3075; (*f*) S. K. Rabindran, H. He, M. Singh, E. Collins, K. I. Annable and L. M. Greberger, *Cancer Res.*, 1998, **58**, 5850; (*g*) E. D. Cox and J. M. Cook, *Chem. Rev.*, 1995, **95**, 1797; (*h*) A. Pictet and T. Spengler, *Ber. Dtsch. Chem. Ges.*, 1911, **44**, 2030.

12 (*a*) F. C. Frebault and N. S. Simpkins, *Tetrahedron*, 2010, **66**, 6585; (*b*) T. J. Greshock and R. M. Williams, *Org. Lett.*, 2007, **9**, 4255; (*c*) L. A. Adams, M. W. N. Valente and R. M. Williams, *Tetrahedron*,

2006, **62**, 5195; (*d*) C. A. Mateo, A. Urrutia, J. G. Rodríguez, I. Fonseca and F. H. Cano, *J. Org. Chem.*, 1996, **61**, 810; (*e*) R. M. Williams, T. Glinka, E. Kwast, H. Coffman and J. K. Stille, *J. Am. Chem. Soc.*, 1990, **112**, 808; (*f*) R. M. Williams, T. Glinka and E. Kwast, *J. Am. Chem. Soc.*, 1988, **110**, 5927; (*g*) J. D. Phillipson and N. Supavita, *Phytochemistry*, 1983, **22**, 1809.

13 For studies of water effect in gold catalysis, see: (*a*) F.-Q. Shi, X. Li, Y. Xia, L. Zhang and Z.-X. Yu, *J. Am. Chem. Soc.*, 2007, **129**, 15503; (*b*) A. S. Dudnik, Y. Xia, Y. Li and V. Gevorgyan, *J. Am. Chem. Soc.*, 2010, **132**, 7645; (*c*) R. Döpp, C. Lothschütz, T. Wurm, M. Pernpointner, S. Keller, F. Rominger and A. S. K. Hashmi, *Organometallics*, 2011, **30**, 5894; (*d*) N. Ghosh, S. Nayak and A. K. Sahoo, *J. Org. Chem.*, 2011, **76**, 500; (*e*) Y. Xia, A. S. Dudnik, Y. Li and V. Gevorgyan, *Org. Lett.*, 2010, **12**, 5538; (*f*) K. Ando, *J. Org. Chem.*, 2010, **75**, 8516; (*g*) A. Rossin, L. Gonsalvi, A. D. Phillips, O. Maresca, A. Lledós and M. Peruzzini, *Organometallics*, 2007, **26**, 3289; (*h*) C. M. Krauter, A. S. K. Hashmi and M. Pernpointner, *ChemCatChem*, 2010, **2**, 1226.

14 For selected theoretical studies of the effect of water in other systems, see: (*a*) Y. Xia, Y. Liang, Y. Chen, M. Wang, L. Jiao, F. Huang, S. Liu, Y. Li and Z.-X. Yu, *J. Am. Chem. Soc.*, 2007, **129**, 3470; (*b*) Y. Liang, H. Zhou and Z.-X. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 17783; (*c*) F.-Q. Shi, *Org. Lett.*, 2011, **13**, 736.

15 For recent examples of DFT studies in gold catalysis, see: (*a*) A. S. K. Hashmi, M. Pernpointner and M. M. Hansmann, *Faraday Discuss.*, 2011, **152**, 179; (*b*) O. N. Faza, C. S. López and A. R. de Lera, *J. Org. Chem.*, 2011, **76**, 3791; (*c*) E. Tkatchouk, N. P. Mankad, D. Benitez, W. A. Goddard and F. D. Toste, *J. Am. Chem. Soc.*, 2011, **133**, 14293; (*d*) R. Fang, C.-Y. Su, C. Zhao and D. L. Phillips, *Organometallics*, 2009, **28**, 741; (*e*) G. Kovács, A. Lledós and G. Ujaque, *Angew. Chem., Int. Ed.*, 2011, **50**, 11147; (*f*) C. Nieto-Oberhuber, P. Pérez-Galán, E. Herrero-Gómez, T. Lauterbach, C. Rodríguez, S. López, C. Bour, A. Rosellón, D. J. Cárdenas and A. M. Echavarren, *J. Am. Chem. Soc.*, 2008, **130**, 269; (*g*) G. Lemière, V. Gandon, K. Cariou, A. Hours, T. Fukuyama, A.-L. Dhimane, L. Fensterbank and M. Malacria, *J. Am. Chem. Soc.*, 2009, **131**, 2993; (*h*) A. Correa, N. Marion, L. Fensterbank, M. Malacria, S. P. Nolan and L. Cavallo, *Angew. Chem., Int. Ed.*, 2008, **47**, 718; (*i*) O. N. Faza, C. S. López, R. Álvarez and A. R. de Lera, *J. Am. Chem. Soc.*, 2006, **128**, 2434; (*j*) R. Fang, L. Yang and Y. Wang, *Org. Biomol. Chem.*, 2011, **9**, 2760; (*k*) L. Yang, R. Fang and Y. Wang, *Comput. Theor. Chem.*, 2011, **965**, 180; (*l*) Y.-X. Liu, D.-J. Zhang and S.-W. Bi, *J. Phys. Chem. A*, 2010, **114**, 12893; (*m*) Y. Xia and G. Huang, *J. Org. Chem.*, 2010, **75**, 7842; (*n*) M. Pernpointner and A. S. K. Hashmi, *J. Chem. Theory Comput.*, 2009, **5**, 2717; (*o*) G. Huang, B. Cheng, L. Xu, Y. Li and Y. Xia, *Chem.–Eur. J.*, 2012, **18**, 5401.

16 We calculated a π complex of **A** and neutral $(PH_3)AuOTf$, but this complexation process is endergonic by 12.1 kcal mol^{-1}, and further C2-site and C3-site annulations require activation barriers of 15.6 and 17.4 kcal mol^{-1}, respectively.

17 See the ESI† for details.

18 Y. J. Hong and D. J. Tantillo, *Organometallics*, 2011, **30**, 5825.

19 A. M. M. Castro, *Chem. Rev.*, 2004, **104**, 2939.

20 (*a*) G. Alagona, C. Ghio and P. I. Nagy, *Phys. Chem. Chem. Phys.*, 2010, **12**, 10173; (*b*) G. Huang, Y. Xia and Y. Li, *THEOCHEM*, 2009, **896**, 80.

21 (*a*) M. Jiang, L.-P. Liu, M. Shi and Y. Li, *Org. Lett.*, 2010, **12**, 116; (*b*) G. Kovács, A. Lledós and G. Ujaque, *Organometallics*, 2010, **29**, 3252; (*c*) G. Kovács, A. Lledós and G. Ujaque, *Organometallics*, 2010, **29**, 5919; (*d*) G. Kovács, G. Ujaque and A. Lledós, *J. Am. Chem. Soc.*, 2008, **130**, 853; (*e*) Y. Xia, A. S. Dudnik, V. Gevorgyan and Y. Li, *J. Am. Chem. Soc.*, 2008, **130**, 6940; (*f*) J. Zhang, W. Shen, L. Li and M. Li, *Organometallics*, 2009, **28**, 3129; (*g*) R.-X. Zhu, D.-J. Zhang, J.-X. Guo, J.-L. Mu, C.-G. Duan and C.-B. Liu, *J. Phys. Chem. A*, 2010, **114**, 4689; (*h*) X. Li, S. Ye, C. He and Z.-X. Yu, *Eur. J. Org. Chem.*, 2008, **25**, 4296.

22 The transformation of intermediate **B-IN6** into the final product by water-cluster-catalyzed H-migrations is very easy†.

23 G. S. Hammond, *J. Am. Chem. Soc.*, 1955, **77**, 334.

24 M. J. Frisch, *et al. GAUSSIAN 09 (Revision A.01)*, Gaussian, Inc., Wallingford CT, 2009. Full citation of Gaussian 09 is given in the ESI†.

25 (*a*) D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648; (*b*) A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 1372; (*c*) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785.

26 (*a*) W. J. Hehre, R. Ditchfield and J. A. Pople, *J. Chem. Phys.*, 1972, **56**, 2257; (*b*) P. C. Hariharan and J. A. Pople, *Theor. Chim. Acta*, 1973, **28**, 213.

27 (*a*) P. J. Hay and W. R. Wadt, *J. Chem. Phys.*, 1985, **82**, 270; (*b*) W. R. Wadt and P. J. Hay, *J. Chem. Phys.*, 1985, **82**, 284; (*c*) P. J. Hay and W. R. Wadt, *J. Chem. Phys.*, 1985, **82**, 299.

28 (*a*) C. Gonzalez and H. B. Schlegel, *J. Chem. Phys.*, 1989, **90**, 2154; (*b*) C. Gonzalez and H. B. Schlegel, *J. Phys. Chem.*, 1990, **94**, 5523.