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Dual Gold-Catalyzed Cycloaromatization of Unconjugated (E)-Enediynes

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COMMUNICATION

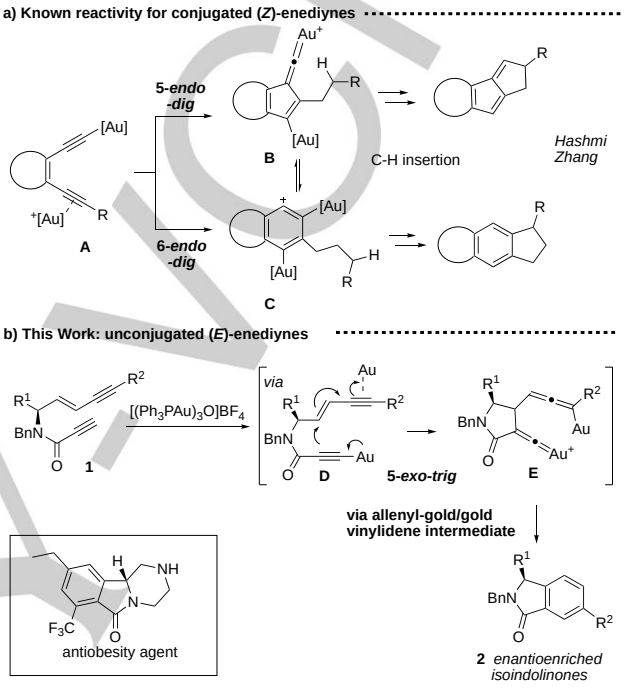
Dual Gold-Catalyzed Cycloaromatization of Unconjugated (*E*)-Enediynes

Farzad Zamani,[a] Rasool Babaahmadi,[b] Brian F. Yates,[b] Michael G. Gardiner, [b] Alireza Ariafard,[b] Stephen G. Pyne,*[a] and Christopher J. T. Hyland*[a]

Abstract: A synthesis of novel unconjugated (*E*)-enediynes from allenyl amino alcohols is reported and their gold-catalyzed cascade cycloaromatization to a broad range of enantioenriched substituted isoindolinones have been developed. Experimental and computational studies support the reaction proceeding via a dual-gold σ,π-activation mode involving a key gold-vinylidene and allenyl-gold-containing intermediate.

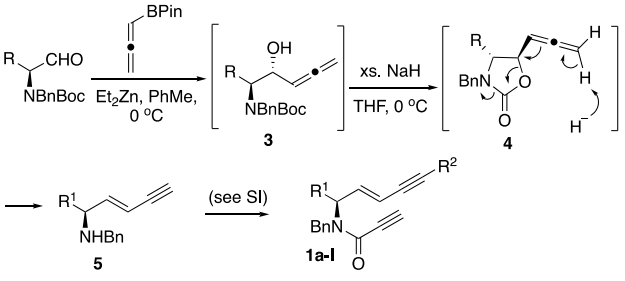
Cycloaromatization reactions of conjugated enediynes is an emerging powerful tool for the synthesis of (hetero)aromatics.[1] Due to the importance of heteroaromatics in bioactive molecules, further advances in this field are important and rely upon uncovering new mechanistic modes of cycloaromatization reactions. In pioneering work by Hashmi[2] and Zhang,[3] gold-catalysed cyclisations of (*Z*)-enediynes have led to highly efficient formation of a range of fused-aromatic structures. These reactions have been proposed to proceed via gold σ,π-dual-activation chemistry – or dual-gold catalysis.[4] Such processes typically involve generation of intermediates **A**, which contain a nucleophilic gold-acetylide that can undergo reaction with an alkyne unit activated by π-binding to cationic gold (Scheme 1a). Species **A** partakes in a bifurcation mechanism where 5-*endo*-dig or 6-*endo*-dig cyclization provides highly electrophilic intermediates **B** and **C** respectively – these then undergo productive chemistry, such as C−H insertion reactions to yield fused polycyclic structures.

We envisioned that an alternative dual-gold cycloaromatization process could be possible if non-conjugated (*E*)-enediynes, such as **1** were employed (Scheme 1b). Doubly activated intermediate **D** might be expected to undergo an alternative 5-*exo*-trig cyclization manifold to yield a highly reactive intermediate **E** comprising gold-vinylidene and allenyl-gold moieties. Given the juxtaposition of a nucleophilic allenyl-gold moiety and the electrophilic gold-vinylidene, their rapid intramolecular reactivity should be expected. Curiously, while gold-vinylidene species have been widely postulated as intermediates in a range of gold-catalysed processes,[5] σ-gold allenyl moieties are almost unknown apart from two recent reports where they have been isolated.[6] As such, a reaction where they can be generated as key intermediates is of fundamental importance. The very limited exploration of unconjugated enediynes, such as **1** is likely in part to a lack of methods for their preparation.[7] Therefore, we report here the synthesis of enantiomerically enriched (*E*)-enediynes **1** and show that they can undergo cascade cycloaromatization reactions via a gold σ,π-dual-activation pathway supported by computational mechanistic studies to afford enantioenriched isoindolinones **2** (Scheme 1b). Critically, the isoindolinone moiety is highly valuable due to its occurrence in numerous bioactive molecules (Scheme 1).[8,9] Despite this, in comparison to other important bioactive heterocyclic skeletons, there are relatively few routes to isoindolinones in enantioenriched[10] or racemic form.[11][12]



Scheme 1. (a) Known reactivity of conjugated (*Z*)-enediynes. (b) Proposed reactivity of unconjugated (*E*)-enediyne via cascade cycloaromatization towards isoindolinones.

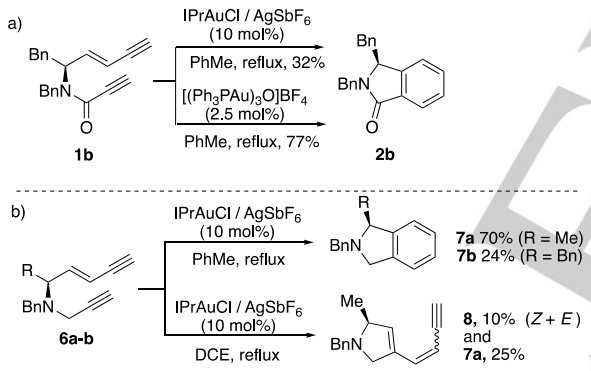
In order to prepare the required (*E*)-enediynes substrates, we turned to our previously reported Zn-catalysed allenylation reaction of doubly protected α-amino aldehydes to give allenyl amino-alcohols **3**.[13] It was found here that these could be directly converted, without isolation, into novel 1,3-(*E*)-enynes **5** in high multi-step yields upon treatment with excess sodium hydride (Scheme 2). This reaction likely proceeds via *in-situ* formation of allenyloxazolidinone **4**,[14] followed by a decarboxylative conjugate elimination.[15] Chiral HPLC analysis of **5a** (R = Me) compared to a racemic standard showed that there is no loss of enantiopurity following the elimination process (*ee* > 99%). Enediynes **1a-l**, where then readily prepared by coupling with propiolic acid or by Sonogashira coupling followed by propiolic acid coupling (Scheme 2 and SI).



Scheme 2. Synthesis of 1,3-(*E*)-enynes and corresponding unconjugated-(*E*)-enediynes.

Enediyne **1b** was used to investigate the proposed cascade cycloaromatization and we were delighted to find that isoindolinone **2b** could be obtained upon treatment of **1b** with IPrAuCl/$AgSbF_6$ (Scheme 3a).[16] Further optimization revealed that inherently basic trigold oxo complex $[(Ph_3PAu)_3O]BF_4$ gave the desired product **2b** in higher yield when compared to IPrAuCl/$AgSbF_6$ – which might be expected if formation of a gold acetylide was taking place. Control experiments in the absence of catalyst (reflux in toluene) showed only trace conversion to **2a**, indicating an uncatalyzed thermal [4 + 2] process is not occurring. [7h] In addition, heating of enediyne **2a** at reflux in toluene with catalytic Tf_2NH resulted in only trace conversion to isoindolinone, pointing away from a Brønsted acid-catalyzed process.

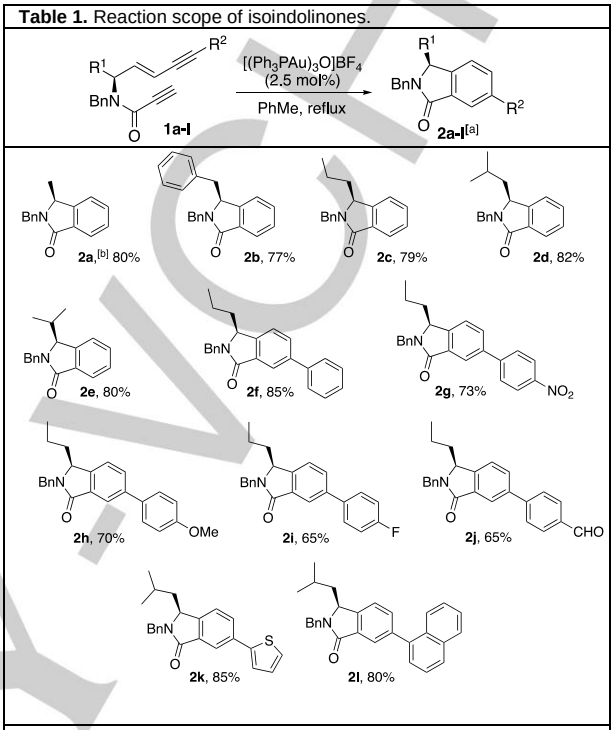
It was found that the propargylated enediynes **6a-b** (preparation in SI) could undergo cycloaromatization, but this reaction was capricious and highly variable low yields were obtained upon repetition due to apparent instability of the isoindoline product. This observation is potentially due to auto-oxidation, which has been previously observed with these heterocycles.[17,18] Running the reaction at lower temperatures in DCE led to the detection of unstable intermediate **8** as a (*Z*/*E*) mixture[19] – providing some indication that a skeletal, rather than a dual-gold mechanism might be one potential pathway operating for the propargyl enediyne substrates, as intermediates **8** are setup to form the isoindole heterocycles via a mono-gold-catalysed cycloaromatization process.[20] These results indicate that the propiolic amide is important for generating a stable organic product and as explained below likely assists in favouring the proposed dual-gold mechanism.



Scheme 3. Preliminary results for the Au(I)-catalysed cycloaromatization of (*E*)-enediynes **1** and **6**.

With the optimized reaction conditions in hand, a range of other amino acid-derived (*E*)-enediynes was evaluated in the novel cycloaromatization process (Table 1). In all cases **1a-e**, high yields of the expected isoindolinones were successfully obtained. Importantly, chiral HPLC analysis of isoindolinone **2a** against a racemic standard showed that it had an *ee* > 99%, demonstrating that loss of stereochemical integrity did not take place under the reaction conditions. To further explore the scope of the protocol with respect to substituents on the terminal alkyne of the enyne unit, a wide range of (*E*)-enynes were synthesised via Sonogashira coupling (Scheme 2) and then coupled with propiolic acid to give (*E*)-enediynes **1f-l** (Scheme 2). From substrates with a phenyl group bearing electron-donating or electron-withdrawing substituents, the corresponding isoindolinone products **2f-l** were obtained in moderate to high yields (Table 1). Halogen and aldehyde substituents were also accommodated by the reaction (products **2i** and **2j**). Further, enediynes **1k** and **1l** bearing thiophene and naphthalene rings were also well tolerated, providing the isoindolinones **2k** and **2l** in high yields. Critically, a single regioisomer of the isoindolinone products was obtained with the aryl group in the 6-position as confirmed by X-ray single crystal structure analysis (for **2h**) and NMR analysis.[21]

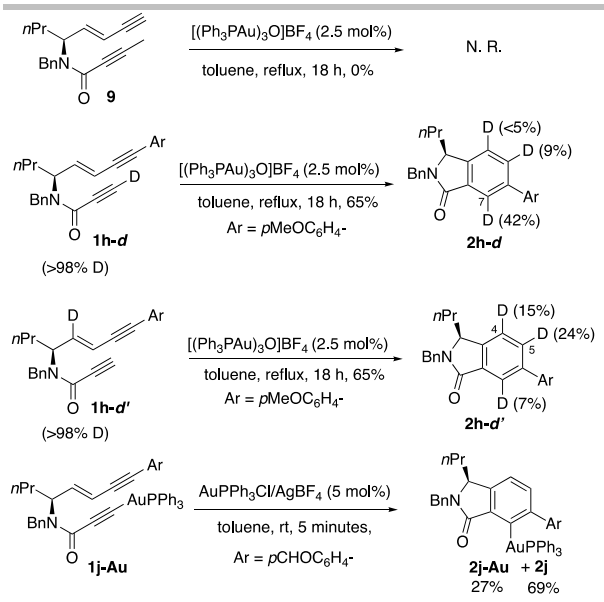
Table 1. Reaction scope of isoindolinones.



[a] Isolated yield. [b] Enantiomeric excess (*ee*) of **2a** was determined as >99% using chiral HPLC analysis (see Supporting Information). CCDC number for **2h**: 1867833

To obtain information about the mechanism of the reaction – and to lend support to the dual-gold catalysis hypothesis – a series of mechanistic experiments were conducted (Scheme 4). First, the necessity of a terminal propiolic amide to form a gold-acetylide intermediate was verified when enediyne **9** failed to undergo reaction under the optimised conditions (Scheme 4). A comparison between gold catalysts showed that the *N*-heterocyclic carbene based catalyst system IPrAuCl/$AgSbF_6$ is significantly less effective than the tris(phosphinegold)oxonium complex $[(Ph_3PAu)_3O]BF_4$ in promoting the reaction (Scheme 3a). These two observations suggest that the intrinsically basic $[(Ph_3PAu)_3O]BF_4$ is promoting deprotonation of the terminal propiolic amide to form a gold acetylide.

Next, deuterated **1h-*d*** and **1h-*d'*** were synthesised and their reactivity under the cycloaromatization conditions was examined (Scheme 4). While significant deuterium loss was observed for **2h-*d***, 42% deuterium remained at the C-7 position in the product, with only minor incorporation at C4/C5. In contrast, subjecting **1h-*d'*** to the gold-catalysis conditions resulted in deuterium incorporation at predominantly C4 and C5 for **2h-*d'***, with relatively little at C7. Furthermore, the regiochemistry of the products **2f-l** is exclusively with the aryl group in the 6-position. This result also points away from a skeletal rearrangement mechanism via intermediates of type **8** (Scheme 3b), as the aryl substituent in the corresponding isoindolinone product might be expected instead to end up at the 4-position. The gold-acetylide **1j-Au** was easily prepared at room temperature (see, SI) and upon treatment with catalytic cationic gold converted in minutes to gold-aryl complex **2j-Au** and **2j** providing further evidence for a dual-gold pathway.



Scheme 4. Mechanistic studies.

Consideration of all these results and subsequent analysis by DFT calculations led us to propose a mechanism for the new cascade cycloaromatization (Figure 1). Initially, the trigold oxo complex coordinates to the enediyne in an endergonic process to form **F**. Binding of the gold catalyst to the triple bond of the enyne (**F**') is disfavoured as the tri-gold oxo complex was calculated to coordinate 2.3 kcal/mol more strongly to a carbonyl-bonded alkyne than to a vinyl-bonded alkyne. This result is consistent with our expectations as these complexes are stabilised by both donation and back-donation interactions. Since the carbonyl group has the greater π-accepting ability compared to the vinyl group, the carbonyl-bonded alkyne is more susceptible to bind the tri-gold oxo complex. The partial Mullikan charge on the enediyne moiety in complex **F** is calculated to be very close to zero (+0.03), confirming our claim that both donation and back donation make determinant contributions to the stability of such an intermediate. A stepwise pathway via a cyclopropyl gold-carbene is therefore unlikely as the coordinated triple bond is not activated towards nucleophilic attack by the enyne double bond.[22]

Intramolecular deprotonation of gold-activated species **F** is energetically favoured leading to the relatively stable gold-acetylide intermediate **G**. An energetically uphill sequence is then necessary – commencing with the digold hydroxide complex dissociating from **G** and forming the Brønsted basic L-Au-OH and Lewis-acidic cationic gold LAu^+ via gold acetylide **H**. The LAu^+ then activates the triple bond of the enyne moiety of the gold-acetylide by π-coordination in highly reactive intermediate **D**. This key intermediate can then cyclize by intramolecular nucleophilic attack of the gold-acetylide onto the activated enyne to afford **E** *via* **TS1** with an energy barrier of 9.5 kcal/mol. Conversely, an alternative cyclisation of the gold acetylide **H** in the absence of coordination to cationic gold has to proceed via a higher energy transition state **TS1-s**. The intermediate **E** is particularly reactive by virtue of nucleophilic allenyl-gold and electrophilic vinylidene-Au moieties being held in close proximity. A direct or a stepwise pathway to the fused six-membered ring intermediate **J** are both possible and are likely competing with each other. The stepwise pathway proceeds via nucleophilic attack of the allenyl-gold moiety on the vinylidene-Au to give the five-membered gold-carbenoid **I**, which subsequently undergoes ring-expansion and a concomitant gold-shift via **TS2** to give **J**. No intermediate(s) for the direct pathway could be located given the favourable nature of the process. Six-membered intermediate **J** can be converted to the isoindolinone product **2** via several potential pathways. At least one of these needs to include a 1,2 hydride/deuterium transfer to account for the presence of deuterium at the C-4 position of the product **2h-*d'*** (Scheme 4). For example based on calculations for the deuterated substrate **1a-d*'***, the intermediate **J-*d*** can proceed via a 1,2-shift process to afford diaurated **K-*d*** that can then lose H^+ or D^+ with concomitant proto/deutero-deauration to give *gem*-diaurated intermediates **M-(4)*d*** or **M-(5)*d*** with deuterium incorporated at C-4 or C-5, respectively (Figure 1(II)).[23] This step is a potential loss point for deuterium, explaining the incomplete retention observed experimentally. These *gem*-diaurated intermediates proceed towards the final isoindolinone products **2a-*d'*** by conversion to the aryl-gold species **N-(4)*d*** or **N-(5)*d*** by reaction with a new molecule of substrate **1a-d*'*** that concomitantly forms gold-coordinated **O-(3)*d***. Finally, protodemetallation by the terminal propiolamide *sp* proton of **O-(3)*d*** generates the final isoindolinone **2a-*d'*** with deuterium in the 4 or 5-position as well as **D-(3)*d*** to re-join the catalytic cycle. This last protodemetallation step is also supported by the observation that the deuterium in **1h-*d*** is predominantly transferred to the 7-position of isoindolinone product **2h-*d*** (Scheme 4). This is likely because **O-*d*-propiolamide** would transfer its deuterium to this position selectively by deutero-deauration of **N** (Figure 1(II)).

In conclusion, successful implementation of a dual-gold catalyzed cycloaromatization reaction of unconjugated enediynes has enabled a new pathway to form the rare and highly reactive combination of a gold-vinylidene and allenyl-gold in a single reaction intermediate. Extension of this concept to other systems where gold vinylidenes and allenylgold species can be simultaneously generated should lead to the discovery of new interesting chemical reactivity. For example, different tethers between the enyne and propiolic unit can be employed to prepare other fused aromatic structures. Further, it can be concluded that electronic differentiation of the triple-bond motifs in non-conjugated enediynes is a strategy to preferentially form a gold-acetylide at a propiolic unit. This concept should allow design of other electronically differentiated systems with two terminal triple bonds for dual-gold catalyzed processes.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cycloaromatization · dual gold catalysis · isoindolinones · enediynes

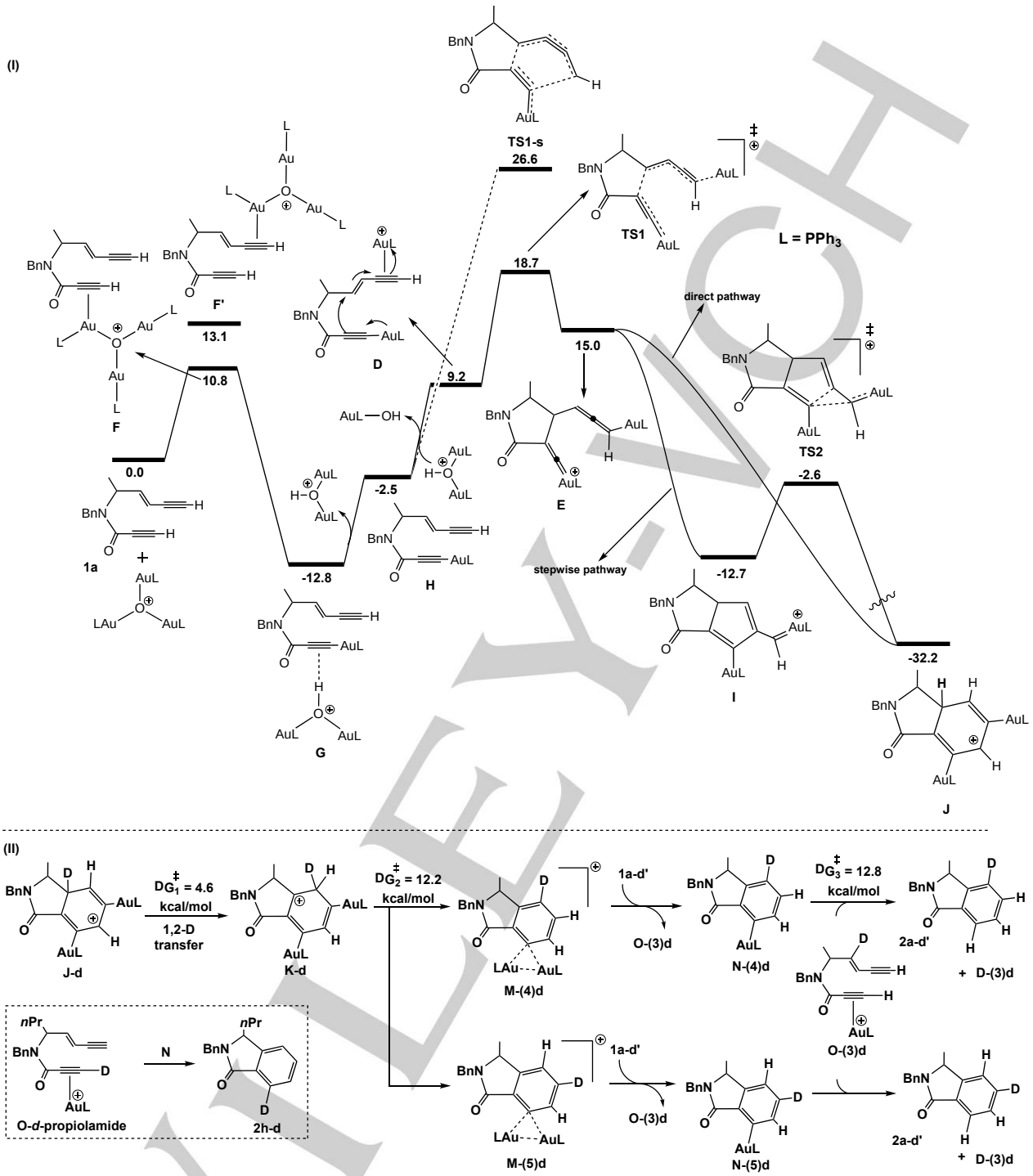

Figure 1. Calculated mechanism for the cascade cycloaromatization reaction. Selected pathway for aromatization and protodemetallation pathways from deuterated **J-*d*** shown in II along with proposed deutero-deauration of **N** by **O-*d*-propiolamide**). The relative Gibbs energies obtained from M06-CPCM/6-31+G(d,p)//B3LYP-CPCM/6-31G(d) calculations are given in kcal/mol.

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[21] Crystal data for **2h**. $C_{25}H_{25}NO_2$ (M_r = 371.46): recorded at 100 K with synchrotron radiation (0.9537 Å), crystal dimensions 0.05 mm x 0.02 mm x 0.02 mm, μ = 0.170 mm^{-1}, monoclinic, space group $P2_1$, a = 8.828(3), b = 5.279(3), c = 20.671(8) Å, β = 91.0640(19) °, V = 963.2(7) Å^3, Z = 2, ρ_{calcd} = 1.281, max/min residuals = 0.129 and -0.136 eÅ^{-3}, Flack parameter = -0.1(3), R = 0.029 for 2210 ($I > 2\sigma(I)$) data and wR = 0.076 for 2231 all data ($2\theta_{max}$ = 64.37 °, R_{int} = 0.050). Data were collected at 100 K on a crystal mounted on a Hampton Scientific cryoloop at the MX2 beamline, Australian Synchrotron, Victoria.[a] The structure was solved by direct methods with SHELXS-97, refined using full-matrix least-squares routines against F^2 with SHELXL-97, [b] and visualised using OLEX2.[c] All non-hydrogen atoms were anisotropically refined, while, all hydrogen atoms were positioned in calculated locations and refined using a riding model with fixed C–H distances of 0.95 Å (sp^2CH), 0.99 Å (CH_2), 0.98 Å (CH_3). The thermal parameters of all hydrogen atoms were estimated as U_{iso}(H) = 1.2U_{eq}(C) except for CH_3 where U_{iso}(H) = 1.5U_{eq}(C). CCDC 1867833 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. [a] T. M. McPhillips, S. E. McPhillips, H. J. Chiu, A. E. Cohen, A. M. Deacon, P. J. Ellis, E. Garman, A. Gonzalez, N. K. Sauter, R. P. Phizackerley, S. M. Soltis, P. Kuhn, *J. Synchrotron Rad.*, **2002**, *9*, 401-406. [b] G. M. Sheldrick, *Acta Cryst.*, **2015**, *C71*, 3-8. [c] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Cryst.*, **2009**, *42*, 339-341.
[22] We thank a referee for suggesting this alternative pathway. For examples of [4 + 2] cycloaddition reactions of dienyne-type substrates that do proceed via gold-catalyzed formation of cyclopropyl carbenes, see: a) S. M. Kim, J. H. Park, Y. K. Chung, *Chem. Commun.* **2011**, *47*, 6719–6721. b) C. Nieto-Oberhuber, S. López, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179.
[23] See the Supplemental Information for calculations for the system bearing an aryl substituent.