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Gold-Catalyzed Annulations of 1-(2,3-Butadienyl)-1*H*-Indole Derivatives

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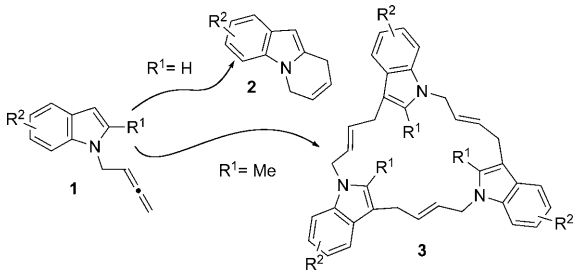
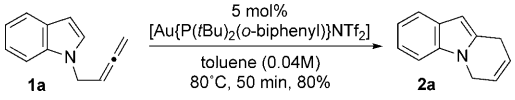
The discovery of catalytic functionalization reactions of privileged heterocyclic scaffolds holds major interest. The vast prevalence and biological significance associated with the indole ring has led to its definition as "The Lord of Rings" at the time of reviewing advances towards its catalytic functionalization,[1] Indole is also a key compound for the study of new arylation strategies,[2] and the search for transition metal-catalyzed preparations and modifications of this heterocyclic core remains an active research area.[3,4] Gold-catalyzed organic reactions are subject of major attention,[5] and powerful modifications of indole based on gold catalysis have been disclosed.[6] Widenhoefer and his group reported advances in the activation of indole towards allene in hydroarylation reactions, and proved useful catalysts to accomplish this goal.[7] Thus, cyclization of 2-allenyl derivatives of *N*-methyl indole following 6- and 7-*exo*-cyclization modes and yielding C3 functionalized annulated compounds are now well documented. Herein, recent findings on gold(I)-catalyzed cyclization reactions of 1-(2,3-butadienyl)-1*H*-indole derivatives are reported, as graphically outlined in Scheme 1.

This study originates from our interest in both indole chemistry[8] and electrophilic arylation of allenes.[9] In addition, the catalytic 6-*endo* allene hydroarylation reaction has been introduced[10–12] and is considerably less studied than the related 6-*exo* cyclization.[13] On this basis, we picked the *N*-tethered 2,3-butadienyl 1*H*-idole **1a** as a model to explore the catalytic 6-*endo* cycloisomerization process.[14] Gratifyingly, exposure of **1a** to gold(I) catalysis resulted in its clean conversion to 6,9-dihydro-pyrido[1,2-*a*]-1*H*-indole (**2a**) (Scheme 2).



Scheme 1. Gold(I)-catalyzed annulations of allenylindoles **1**.



Scheme 2. Cycloisomerization via 6-*endo* allene hydroarylation giving isolable pyrido[1,2-*a*]-1*H*-indole derivatives.

The ancillary ligand was selected considering precedents for catalytic allene hydroarylation reactions. Triphenylphosphine[13d] and di-*tert*-butyl(*ortho*-biphenyl)phosphine, [P-(*t*Bu)$_2$(*o*-biphenyl), JOHNPHOS][7,10a] were chosen. As the counteranion for gold(I), bis(trifluoromethanesulfonyl)imidate (NTf_2) appeared to be an interesting choice. As early pointed out by Gagosz, it behaves similar to other weakly coordinating anions and avoids addition of a silver(I) salt to render a more electrophilic gold center, a process typically associated with alternative chloride precatalyst.[15]

For **1a**, higher yield of **2a** and shorter reaction times were noticed in the gold-catalyzed reaction with the Buchwald-type biaryl ligand than with related triphenylphosphine.[16] At room temperature, the cyclization also took place, but required longer reaction time to get a similar yield. This efficient cyclization led to a clean isolation of the assembled pyrido[1,2-*a*]-1*H*-indole scaffold, adding preparative interest to the process. Moreover, the obtained pyridoindole is a significant heterocyclic scaffold.[17] The scope of the process concerning the indole substitution was investigated in this preliminary study and is outlined in Table 1. Interestingly,

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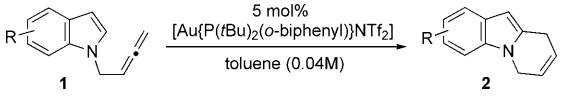
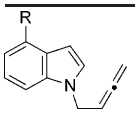
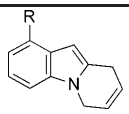
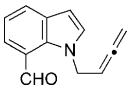
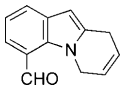
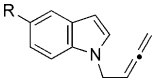
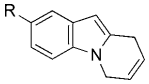
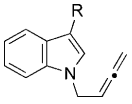
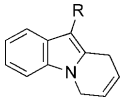
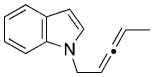
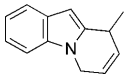
Table 1. Gold-catalyzed 6-*endo* cyclosiomerization of allenylindoles.



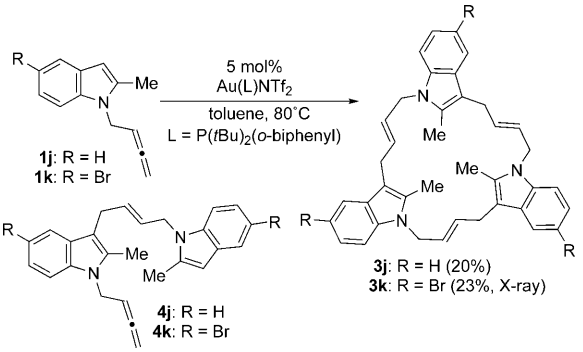
Allenylindole **1**	T [°C]	t [h]	Product **2**	Yield [%][a]
				
1b: R = OMe	80	1	**2b**: R = OMe	89
1c: R = Br	80	1.5	**2c**: R = Br	79
				
1d	80	3	**2d**	86
				
1e: R = Br	80	1.5	**2e**: R = Br	87
1f: R = 4-MeO-C_6H_4	80	16	**2f**: R = 4-MeO-C_6H_4	60
				
1g: R = Me	20	1	**2g**: R = Me	93[b]
1h: R = CHO	120	8	**2h**: R = CHO	78[c]
				
1i	65	16	**2i**	71

[a] Isolated yield upon chromatographic purification. [b] Reaction using [$Ph_3PAuNTf_2$]. [c] Reaction at 80 °C for 15 h resulted in the formation of **2h** in comparable yield.

this cyclization shows broad functional group tolerance. Thus, contrary to the scope found in the precedents, this cyclization is not restricted to the case of strong electron-donor substituents. Thus, far from activating groups (strong OMe or weak Me, aryl), this catalytic reaction is nicely compatible with weak (Br) or even more strong (CHO) deactivators. These substituents were tested at different positions in indole, with satisfactory results in all cases. The cyclization was also efficient for an internal allene (**1i**), suggesting interesting opportunities for subsequent developments in this context.

Interestingly, this cycloisomerization entails a catalytic C–H functionalization of indole that takes place overriding a strong competitive intermolecular activation of the more nucleophilic indole C3 position towards an electrophilic activation. To validate this assumption we explored related systems bearing an alkyl substituent at indole ring C2 position. Thus, reactions of methyl indole derivatives **1j** and **1k** were investigated (Scheme 3).

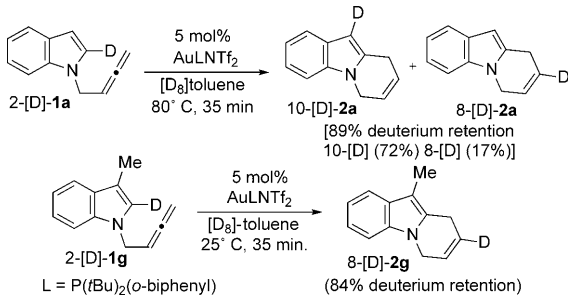
Under the initial conditions used substantial polymerization occurred. However, a careful control of the experimental protocol, specifically the reaction time and the concentration, enabled the isolation of well-defined adducts, although in modest yield. Thus, **1j** (R = H, reaction for 9 h, 3×10^{-2} M) and **1k** (R = Br, 16 h, 2×10^{-2} M) gave **3j** and **3k**, respectively. This type of cyclization is clearly different from



Scheme 3. Cyclotrimerization of 2-substituted *N*- allenylindoles.

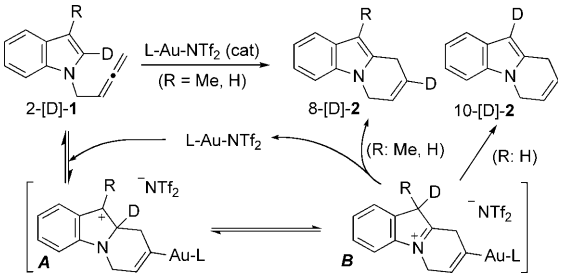
the early noticed clean cycloisomerization process. The alternative formation of these macrocyles can be rationalized assuming initial allene activation by the carbophilic catalyst, followed by trapping of the resulting cationic species by indole, involving now the usual nucleophilic C3 position. This process keeps evolving to give a macrocycle.[18] Allyl-homologated indolo-cyclotriveratrylene analogs with a distinctive 1,3′-linkage were accessed.[19] The proposed stepwise nature for this trimerization is consistent with the isolation of the dimer **4j** (14%) from the crude mixture leading to **3j**. Also, tiny amounts of an open-chain trimer **5j** were isolated from the same reaction crude, and further provided support to this hypothesis.[20] Furthermore, **4k** was synthesized in 25% yield using alternative experimental conditions to those used in the preparation of **3k**.[21]

Upon confirming the key role of the substitution pattern at the indole C2 position, additional experiments were conducted to gain mechanistic insight into the formation of heterocycles **2**. As depicted in Scheme 4, 2-deutero derivatives of **1a** and **1g** were prepared and subjected to the cycloisomerization conditions, and gave deuterated **2a** and **2g**, respectively. These products show the deuterium label mostly attached at a different ring position. Thus, while for **2a** deuterium was incorporated at two different positions (C10 and C8),[22,23] only one deuterated cyclization product was noticed for **2g**. A direct sequence based on electrophilic cyclization, proton elimination and protonolysis of the C–Au bond by the generated acid, though in agreement with cycli-



Scheme 4. Cycloisomerization of deuterated **1a** and **1g**: differential labelling, as revealed by NMR monitoring of the reaction.

zation of deuterated **1g**, is not consistent with the observed deuterium distribution in the reaction of **1a**. Furthermore, a control experiment conducted exposing either **1a** or **1g** to the gold catalyst in [D_8]toluene, at 80 °C, afforded **2a** and **2g**, respectively, without deuterium incorporation. Moreover, 2-deutero-1-methyl-1*H*-indole was treated with the gold catalyst and the process monitored NMR. No evidence for scrambling of deuterium between C2 and C3 was gathered.[24] In another NMR experiment, **1a** (0.04 M in [D_8]toluene) remained unaltered after treatment for 12 h, at room temperature, with triflimide ($HNTf_2$, 20 mol %). Also, lack of cyclization was noticed after a related reaction for 8 h at 80 °C though, in this case, partial decomposition began to be observable. On this experimental basis, a tentative mechanistic description is outlined in Scheme 5.



Scheme 5. Isomerization of **1** to **2**: working mechanistic hypothesis.

This proposal assumes an initial interaction of cationic gold(I) with the allene to give a π-complex. A subsequent slippage of gold through the unsaturation would afford a cationic intermediate, with gold attached to the central carbon of the former allene, that is a suitable species to attack the indole ring.[25] The topology of the substrate would override the incorporation of this electrophile at the indole C3 position, otherwise a usual process, because of the high strain associated with this cyclization. This allows an alternative pyrrole-like reactivity to be observed and, as a consequence, cyclization at the indole C2 position occurs. Next, the cyclization would yield intermediate **A**, that developed a positive charge at C3 as result of the electrophilic ring-closure.[26] It might evolve to enjoy stabilization by the lone pair of electrons residing at nitrogen without disrupting the aromaticity of the benzene moiety to afford a cationic species **B** that,[27] ultimately, would aromatize and furnish cyclization product **2**, showing the observed deuterium distribution.

Although alternative proposals could be discussed they seem less likely on the basis of the data available. In this regard, driven by initial coordination of gold to the allene,[28] a selective electrophilic auration at C2 could be invoked and different ways for its conversion to **2** envisaged. However, the product distribution observed for the reaction of deuterated **1a**, and the experimentally determined value for the primary kinetic isotopic effect [PKIE, k_H/k_D (**1a**, 25 °C) = 1.10, and k_H/k_D (**1g**, 25 °C) = 1.04] are difficult to harmonize to this alternative mechanistic picture.[29] Finally, product formation based on the direct electrophilic auration of the reactive indole C3 position, competitively with the assumed key allene π-activation, can not be safely ruled out at present.[30]

In summary, well-defined examples of a catalytic allene hydroarylation following the 6-*endo* cyclization mode are presented. The methodology is applied in a straight synthesis of the relevant 6,9-dihydro-pyrido[1,2-*a*]-1*H*-indole core. Substitution at C2 in the indole moiety precludes the cycloisomerization to occur and rather, a careful control over the reaction conditions drives an interesting cyclotrimerization reaction furnishing macrocyclic compounds. Moreover, experimental work done to scrutinize this new transformation revealed valuable information that add further and distinctive features to this catalytic chemistry and prompt further efforts to uncover mechanistic aspects.

Experimental Section

Typical procedure for the gold-catalyzed 6-*endo* allene hydroarylation exemplified for 2a: To a solution of 1-(buta-2,3-dienyl)-1*H*-indole (**1a**; 0.2 mmol, 34 mg) in toluene (5 mL, 0.04 M), $JOHNPHOSAuNTf_2$ (5 mmol %, 8 mg) was added under argon atmosphere, at 80 °C. The mixture was stirred for further 50 min at this temperature. Then, the volume of the solution was reduced to ca. 1 mL, by partial removal of solvent under high vacuum. The resulting concentrated solution was charged into a chromatographic column to isolate 6,9-dihydro-pyrido[1,2-*a*]indole (**2a**) [silica gel; hexane/AcOEt/40:1 (R_f = 0.3) as the eluent] as a white solid (27 mg, 80 %; m.p. 136.1–138.3 °C).

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Keywords: allenes · C–H functionalization · cyclization · gold · indoles

[1] a) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786–9824; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644. For a recent example of palladium-catalyzed reaction of indoles with alkynes leading to tetrahydroquinolines: b) Z. Shi, B. Zhang, Y. Cui, N. Jiao, *Angew. Chem.* **2010**, *122*, 4130–4135; *Angew. Chem. Int. Ed.* **2010**, *49*, 4036–4041.

[2] For recent reviews on catalytic arylation reactions of indole and of heteroarenes: a) L. Joucla, L. Djakovitch, *Adv. Synth. Catal.* **2009**, *351*, 673–714; b) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976–10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826.

[3] For selected recent reviews: a) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873–2920; b) K. Krüger (neé Alex), A. Tillack, M.

Beller, *Adv. Synth. Catal.* **2008**, *350*, 2153–2167; c) J. Barluenga, F. Rodríguez, F. J. Fañanás, *Chem. Asian J.* **2009**, *4*, 1036–1048.

[4] For selected recent reviews covering general advances in the synthesis of heterocyclic compounds by using transition metal-catalyzed reactions, see: a) J. J. Li, G. W. Gribble, *Palladium in Heterocyclic Chemistry*, Pergamon, Oxford, **2000**, pp. 73–181; b) G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644–4680; c) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395–3442.

[5] For selected reviews, see: a) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; b) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478–3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; c) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239–3265; d) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266–3325; e) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378; f) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208–3221.

[6] For representative examples: a) L. Zhang, *J. Am. Chem. Soc.* **2005**, *127*, 16804–16805; b) C. Ferrer, C. H. M. Amijs, A. M. Echavarren, *Chem. Eur. J.* **2007**, *13*, 1358–1373; c) R. Sanz, D. Miguel, F. Rodríguez, *Angew. Chem.* **2008**, *120*, 7464–7467; *Angew. Chem. Int. Ed.* **2008**, *47*, 7354–7357; d) M.-Z. Wang, M. -Kin, W. , C.-M. Che, *Chem. Eur. J.* **2008**, *14*, 8353–8364; e) Y. Lu, X. Du, X. Jia, Y. Liu, *Adv. Synth. Catal.* **2009**, *351*, 1517–1522; f) J. Barluenga, A. Fernández, F. Rodríguez, F. J. Fañanás, *Chem. Eur. J.* **2009**, *15*, 8121–8123; g) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9697–9701; *Angew. Chem. Int. Ed.* **2009**, *48*, 9533–9537; h) X. Zeng, R. Kinjo, B. Donnadieu, G. Bertrand, *Angew. Chem.* **2010**, *122*, 954–957; *Angew. Chem. Int. Ed.* **2010**, *49*, 942–945; i) A. S. K. Hashmi, T. D. Ramamurthi, F. Rominger, *Adv. Synth. Catal.* **2010**, *352*, 971–975.

[7] For 6- and 7-*exo*-hydroarylation reactions of 2-allenyl indoles: a) Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Quian, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2006**, *128*, 9066–9073; enantioselective process: b) C. Liu, R. A. Widenhoefer, *Org. Lett.* **2007**, *9*, 1935–1938; intermolecular hydroarylation of allenes with indoles: c) K. L. Toups, G. T. Liu, R. A. Widenhoefer, *J. Organomet. Chem.* **2009**, *694*, 571–575.

[8] a) J. Ezquerra, C. Pedregal, C. Lamas, J. Barluenga, M. Pérez, M. A. García-Martín, J. M. González, *J. Org. Chem.* **1996**, *61*, 5804–5812; b) F. J. Fañanás, A. Granados, R. Sanz, J. M. Ignacio, J. Barluenga, *Chem. Eur. J.* **2001**, *7*, 2896–2907; c) J. Barluenga, M. Trincado, E. Rubio, J. M. González, *Angew. Chem.* **2003**, *115*, 2508–2511; *Angew. Chem. Int. Ed.* **2003**, *42*, 2406–2409; d) J. Barluenga, M. A. Fernández, F. Aznar, C. Valdés, *Chem. Eur. J.* **2005**, *11*, 2276–2283; e) J. Barluenga, H. Vázquez-Villa, A. Ballesteros, J. M. González, *Adv. Synth. Catal.* **2005**, *347*, 526–530; f) J. Barluenga, H. Vázquez-Villa, A. Ballesteros, J. M. González, *Chem. Eur. J.* **2006**, *12*, 5790–5805; g) J. Barluenga, A. Jiménez-Aquino, F. Aznar, C. Valdés, *Angew. Chem.* **2007**, *119*, 1551–1554; *Angew. Chem. Int. Ed.* **2007**, *46*, 1529–1532; h) J. Barluenga, E. Tudela, A. Ballesteros, M. Tomás, *J. Am. Chem. Soc.* **2009**, *131*, 2096–2097; i) J. Barluenga, A. Jiménez-Aquino, F. Aznar, C. Valdés, *J. Am. Chem. Soc.* **2009**, *131*, 4031–4041.

[9] Allene iodoarylation: J. Barluenga, E. Campos-Gómez, A. Minatti, D. Rodríguez, J. M. González, *Chem. Eur. J.* **2009**, *15*, 8946–8950.

[10] a) T. Watanabe, S. Oishi, N. Fuji, H. Ohno, *Org. Lett.* **2007**, *9*, 4821–4824. An interesting gold-catalyzed hydroarylation of *N*-allenyl-*N*-aryl methyl carbamates yielding methyl quinoline-1-(4*H*)-carboxylate derivatives was described. The 1,4-dihydro heterocyclic frame was not characterized. Alternatively, the tetrahydoquinoline resulting from catalytic hydrogenation was isolated and characterized; b) W. Kong, C. Fu, S. Ma, *Chem. Commun.* **2009**, 4572–4574. A nice Pt^{II}-catalyzed cyclization of 1-(indol-2-yl)-2,3-allenols gave carbazoles. It involves a 6-*endo* allene hydroarylation step. The intermediate adduct efficiently evolves under the reaction conditions to give the isolated carbazole; c) J. Mo, P. H. Lee, *Org. Lett.* **2010**, *12*, 2570–2573. While our manuscript was in preparation, this report appear describing the utility of the catalytic $PtCl_2$/AgOTf system to clearly carry out the hydroarylation of ethyl 2-benzyl-2,3-alkadienoates.

[11] For selected 6-*endo* carbocyclizations of allenes with other types of unsaturated motifs: a) T. Miura, K. Kiyota, H. Kusama, K. Lee, H. Kim, S. Kim, P. H. Lee, N. Iwasawa, *Org. Lett.* **2003**, *5*, 1725–1728; b) G. Lemière, V. Gandon, N. Agenet, J.-P. Goddard, A. de Kozak, C. Aubert, L. Fensterbank, M. Malacria, *Angew. Chem.* **2006**, *118*, 7758–7761; *Angew. Chem. Int. Ed.* **2006**, *45*, 7596–7599; c) G.-Y. Lin, C.-Y. Yang, R.-S. Liu, *J. Org. Chem.* **2007**, *72*, 6753—6757; d) R. Chaudhuri, H.-Y. Liao, R.-S. Liu, *Chem. Eur. J.* **2009**, *15*, 8895–8901. For a 7-*endo* cyclization of 1-(2-propa-1,2-dienyl-phenyl)-1*H*-pyrrole at the regular C2 position of pyrrole: e) V. Mamane, P. Hannen, A. Fürstner, *Chem. Eur. J.* **2004**, *10*, 4556–4575.

[12] For representative recent gold-catalyzed 6-*endo-dig* heterocyclization reactions of allenes, see: a) B. Gockel, N. Krause, *Org. Lett.* **2006**, *8*, 4485–4488; b) J. Piera, P. Krumlinde, D. Strübing, J.-E. Bäckvall, *Org. Lett.* **2007**, *9*, 2235–2237; c) C. Winter, N. Krause, *Angew. Chem.* **2009**, *121*, 6457–6460; *Angew. Chem. Int. Ed.* **2009**, *48*, 6339–6342; d) B. Alcaide, P. Almendros, T. Martínez del Campo, E. Soriano, J. L. Marco-Contelles, *Chem. Eur. J.* **2009**, *15*, 9127–9138; e) B. Gockel, N. Krause, *Eur. J. Org. Chem.* **2010**, 311–316.

[13] For a recent review, see: a) H. C. Shen, *Tetrahedron* **2008**, *64*, 3885–3903; b) for the use of indole as arene see reference [7] in this manuscript; for the use of carbocyclic electron-rich arenes, see: c) M. A. Tarselli, M. R. Gagné, *J. Org. Chem.* **2008**, *73*, 2439–2441; d) D. Weber, M. A. Tarselli, M. R. Gagné, *Angew. Chem.* **2009**, *121*, 5843–5846; *Angew. Chem. Int. Ed.* **2009**, *48*, 5733–5736.

[14] The preparation of the starting materials was accomplished adapting known literature procedures to prepare allenes [*Modern Allene Chemistry, Vols. 1 and 2* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**], as detailed in the Supporting Information. Their characterization, those of the cyclization products and details for the mechanistic studies are also included.

[15] a) For the preparation and convenience of gold complexes featuring this anion, see: N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133–4136. For recent uses, see: b) A. Buzas, F. Gagosz, *J. Am. Chem. Soc.* **2006**, *128*, 12614–12615; c) A. Leyva, A. Corma, *J. Org. Chem.* **2009**, *74*, 2067–2074.

[16] The conversion using $Ph_3PAuNTf_2$ was lower than 50%, under the conditions in Scheme 2. Furthermore, compound **1c** (see Table 1) was recovered essentially unreacted after treatment with $Ph_3PAuNTf_2$ in toluene at 80°C for near 6 h.

[17] Representative synthesis of pyrido[1,2-*a*]-1*H*-indoles: a) S. Caddick, K. Aboutayab, R. West, *Synlett* **1993**, 231–232; b) C. J. Moody, C. L. Norton, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2639–2643; c) H. Siebeneicher, I. Bytschkov, S. Doye, *Angew. Chem.* **2003**, *115*, 3151–3153; *Angew. Chem. Int. Ed.* **2003**, *42*, 3042–3044; d) C. Bressy, D. Alberico, M. Lautens, *J. Am. Chem. Soc.* **2005**, *127*, 13148–13149; e) M. Ishikura, W. Ida, K. Yanada, *Tetrahedron* **2006**, *62*, 1015–1024; f) J. Magolan, M. A. Kerr, *Org. Lett.* **2006**, *8*, 4561–4564; g) K. Fuchibe, T. Kaneko, K. Mori, T. Akiyama, *Angew. Chem.* **2009**, *121*, 8214–8217; *Angew. Chem. Int. Ed.* **2009**, *48*, 8070–8073; h) S.-C. Lu, X.-Y. Duan, Z.-J. Shi, B. Li, Y.-W. Ren, W. Zhang, Y.-H. Zhang, Z.-F. Tu, *Org. Lett.* **2009**, *11*, 3902–3905; i) J. W. Tucker, J. M. R. Narayanam, S. W. Krabbe, C. R. J. Stephenson, *Org. Lett.* **2010**, *12*, 368–371.

[18] CCDC-771248 contains the supplementary crystallographic data for compound **3k**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] For a recent synthesis of indolocyclotriveratrylene, see: a) M. Santoso, K. Somphol, N. Kumar, D. StC. Blak, *Tetrahedron* **2009**, *65*, 5977–5983, and references therein. For its bioactivity profile as agonist of the estrogen receptor signalling pathway, see: b) J. E. Riby, C. Feng, Y.-C. Chang, C. M. Schaldach, G. L. Firestone, L. F. Bjeldanes, *Biochemistry* **2000**, *39*, 910–918; c) L. Xue, C. M. Schaldach, T. Janosik, J. Bergman, L. F. Bjeldanes, *Chem.-Biol. Interact.* **2005**, *152*, 119–129.

[20] Compound **5j** was isolated in 5% yield, see the Supporting Information.

[21] For the synthesis of **4k**, reaction temperature was 80°C, the concentration of **1k** was 3×10^{-2} M; 10 mol% of the catalyst was added and the reactions time was extended up to 16 h.

[22] For the NMR experiment, the deuterium retention in **2a** was established considering the excess of the integral for H7 with respect to the corresponding signal for H8 and the information supply by the integral for H10 (for a copy of the spectrum and further details, see the Supporting Information). Control experiments proved that 10-[D]-6,9-dihydro-pyrido[1,2-*a*]-1*H*-indole (**2a**) undergoes D/H exchange in both, deuterated chloroform and toluene solutions of standard grade, as a function of the time. So the integral for H10 may experience appreciable deviations on standing 10-[D]-**2a** in the solvent. Also, attempts to isolate deuterated products **2a** upon routine column chromatography resulted in complete lost of deuterium, though confirm a proper mass balance for the cyclization.

[23] For a related rapid 1,2-shift, involving high deuterium retention yet incomplete, see for instance: A. Fürstner, F. Stelzer, H. Szillat, *J. Am. Chem. Soc.* **2001**, *123*, 11863–11869.

[24] For relevant synthetic studies on C3–C2 metal migration on indole scaffolds, see for instance: a) palladium(II), N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem.* **2005**, *117*, 3185–3189; *Angew. Chem. Int. Ed.* **2005**, *44*, 3125–3129; b) copper(III): R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172–8174; c) for a detailed mechanistic study on the regioselectivity of indole arylation reactions and the role of electrophilic palladation involving palladium-containing indoleninium cations: B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057.

[25] For cationic gold activation of an allene giving rise to an isolable alkenyl–gold intermediate: a) L.-P. Liu, B. Xu, M. S. Mashuta, G. B. Hammond, *J. Am. Chem. Soc.* **2008**, *130*, 17642–17643. For a recent study on isolable vinylgold complexes derived from alkynes: b) A. S. K. Hashmi, A. M. Schuster, F. Rominger, *Angew. Chem.* **2009**, *121*, 8396–8398; *Angew. Chem. Int. Ed.* **2009**, *48*, 8247–8249.

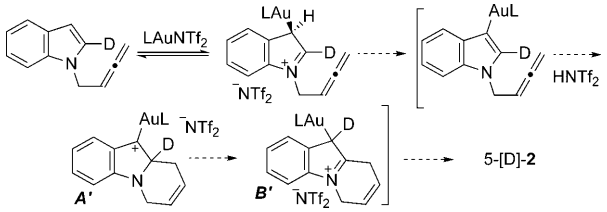
[26] For an authoritative review on electrophilic addition and cyclization reactions of allene, see: S. Ma, *Acc. Chem. Res.* **2009**, *42*, 1679–1688.

[27] Whether this is a true 1,2-deuterium shift or a stepwise process that entails elimination and subsequent competitive neutralization by either the basic C3 indole position or, alternatively, by the carbon–gold bond, is not unequivocally established.

[28] For recent studies on processes involving regioselective directed palladation of indoles at C2 position: a) A. García-Rubia, R. Gómez Arrayás, J. C. Carretero, *Angew. Chem.* **2009**, *121*, 6633–6637; *Angew. Chem. Int. Ed.* **2009**, *48*, 6511–6515; b) E. Capito, J. M. Brown, A. Ricci, *Chem. Commun.* **2005**, 1854–1856; c) for a review on metal complexes involving indole rings: Y. Shimazaki, T. Yajima, M. Takani, O. Yamauchi, *Coord. Chem. Rev.* **2009**, *253*, 479–492.

[29] For aromatic electrophilic substitution reactions, the measured KIE take their value on a wide range. As a result, for some representative reactions, as the case of aromatic nitration, C–H cleavage is not involved in the rate-determining step. However, in a closer process to auration, as it is the case of electrophilic mercuration, a large value consistent with proton-loss occurring at the rate determining step has been recorded: a) A. J. Kresge, J. F. Brennan, *J. Org. Chem.* **1967**, *32*, 752–755; b) C. W. Fung, M. Khorramdel-Vahed, R. C. Ranson, R. M. G. Roberts, *J. Chem. Soc. Perkin Trans. 2* **1980**, 267–272.

[30] Actually, low temperature NMR monitoring for the reaction of **1a** with the gold complex gave preliminary evidence for partial incorporation of the phosphine–gold fragment into C3, yielding the aurated intermediate indoleninium cation, en route to obtain the product of electrophilic aromatic substitution by gold at that position (see the Supporting Information). Then, further allene activation by the generated proton followed by cyclization should render intermediate **A′**, where the carbocation would benefit from stabilization by the attached gold at C3. Subsequent evolution by favorable 1,2-migration of deuterium would account well for the noticed product distribution for **1a**, though it will require a different mechanism operating for **1g**. However, no evidence for a clean and full conversion to C3-aurated compounds, even in the presence of bases or using a model compounds lacking the allene moiety, as *N*-methylindole, were obtained to provide support to this alternative hypothesis (see also ref. [6i]). For important work on a clean conversion of indole into a C3 aurated indolenium cation and for an efficient synthesis of C3 aurated indoles, see above reference [6h].



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