Gold Catalysis

DOI: 10.1002/anie.201205463

One-Pot Gold-Catalyzed Synthesis of Azepino[1,2-*a*]indoles**

*Gianpiero Cera, Stefano Piscitelli, Michel Chiarucci, Giancarlo Fabrizi, Antonella Goggiamani, Rubén S. Ramón, Steven P. Nolan, and Marco Bandini**

Indoles are one of the most abundant heteroaromatic compounds found in nature, and is ranked third (after benzene and pyridine) amongst the most prevalent architectures found in bioactive molecules.[1] In this context, it is not surprising to note a beehive of activity in the development of sustainable methods for the synthesis[2] and functionalization[3] of the indolyl core. Over the past ten years, advances in catalysis have revolutionized the field by bringing unexpected levels of efficiency, selectivity, and sustainability into practice.

However, catalytic methods that simultaneously address synthesis and derivatization of indoles are still far from common.[4] Some leading metal-assisted examples deal principally with the construction of the pyrrolyl ring with a final C3-functionalization through alkylations[5] or cross-coupling reactions.[2d,6] Among them, gold(I)/(III) catalysis has played a major role[7] in generating chemical diversity/complexity under mild and selective conditions.

As a part of our ongoing interest in organo-[8a] and metal-catalyzed synthesis of the indole/indoline polycyclic architectures,[8b–f] we turned our attention to the azepinoindole scaffold, which is commonly encountered in biologically active compounds.[9]

More specifically, azepino[1,2-*a*]indoles, which feature a fused seven-membered ring through the N1–C2 connection, have displayed fascinating pharmacological activities, such as acting in the inhibition of HCV NS5B polymerase (**A**; Figure 1)[10a,b] and as modulators for CNS neurotransmitter receptors (**B**).[10c,d] In the case of this species, although the metal-catalyzed synthesis of 6*H*-azepino[1,2-*a*]indole derivatives has recently been documented,[11] stepwise synthetic sequences starting from a preformed indolyl nucleus are generally necessary to build up the fused polycyclic system.[12]

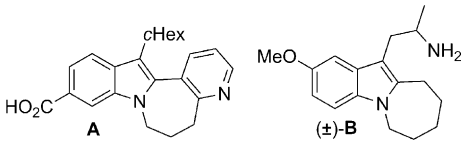
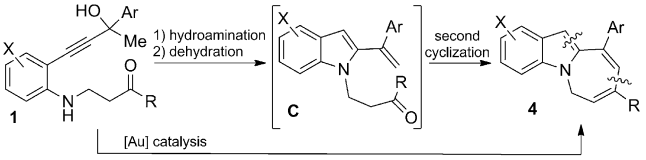


Figure 1. Examples of pharmacologically active azepino[1,2-*a*]indoles. *c*Hex = cyclohexyl.

With the existing laborious and multistep approaches in mind, we herein describe an unprecedented gold-assisted cascade reaction for the synthesis of azepino[1,2-*a*]indoles starting from readily available 2-alkynylanilines. Our working hypothesis was hinged on the suitability of 2-(propargylic alcohol)-anilines (**1**) in providing nucleophilic 2-vinylindole intermediates (**C**) through a gold-triggered *5-endo-dig* hydroamination/dehydration sequence.[13] At this stage, the preinstallation of a complementary (electrophilic) group (such as carbonyl) tethered to the aniline nitrogen atom was thought to allow the second cyclization reaction to take place, providing a N1–C2 fusion to produce the indole core (Scheme 1).

A survey of reaction conditions was carried out to identify the optimal catalytic system, with aniline **1a** as the model substrate (Table 1). Among the metal species utilized



Scheme 1. Proposed reaction sequence.

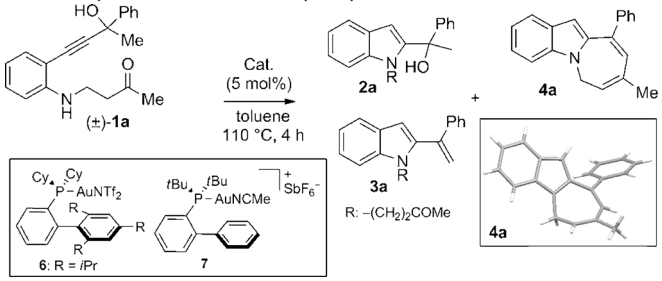
(entries 1–3,5) gold(I) showed the highest catalytic activity. However, indolyl-alcohol **2a** and 2-vinyl-indole **3a** were obtained exclusively in the presence of phosphine-based gold(I) complexes (entries 5–7). The use of an N-heterocyclic carbene (NHC)-bearing system, [Au(IPr)Cl]/$AgBF_4$ (5 mol%; IPr = 1,3-di(isopropylphenyl)imidazol-2-ylidene), in refluxing toluene for 4 h, provided the desired 8-methyl-10-phenyl-6*H*-azepino[1,2-*a*]indole (**4a**) in 34% yield (Table 1, entry 11). As the use of [Au(NHC)] systems is becoming more widespread in organic synthesis,[14] and as the synthetic routes to a series of congeners have been reported, we envisioned the possibility of increasing the chemical yield of the reaction sequence by examining the role of the

[*] G. Cera, S. Piscitelli, Dr. M. Chiarucci, Prof. M. Bandini
Dipartimento di Chimica "G. Ciamician"
Alma Mater Studiorum—Università di Bologna
via Selmi 2, 40126 Bologna (Italy)
E-mail: marco.bandini@unibo.it
Homepage: http://www.mbandini-group.com
Prof. G. Fabrizi, Dr. A. Goggiamani
Dip. di Chimica e Tecnologia del Farmaco Sapienza
Università di Roma (Italy)
R. S. Ramón, Prof. Dr. S. P. Nolan
EaStCHEM School of Chemistry, University of St Andrews (UK)

[**] Acknowledgements are made to the Progetto FIRB "Futuro in Ricerca" *Innovative sustainable synthetic methodologies for C-H activation processes*, (MIUR, Rome) and the Università di Bologna. For support of the work in St. Andrews, the ERC (Advanced Researcher Award FUNCAT to S.P.N.) and the EPSRC are gratefully acknowledged. We also thank Prof. M. Monari for the X-ray analysis of **4a**. S.P.N. is a Royal Society Wolfson Research Merit Award holder.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201205463.

Table 1: Optimization of the catalytic system.[a]



Entry	Cat.	Yield of **2a** [%][b]	Yield of **3a** [%][b]	Yield of **4a** [%][b]
1[c]	$In(OTf)_3$	–	–	–
2[c]	$FeCl_3$	–	–	–
3	AgOTf	–	23	–
4[c]	TfOH	–	–	–
5	$[Au(PPh_3)NTf_2]$	64	36	–
6[d]	$[(AuNTf_2)_2dppf]$	15	–	–
7[d]	$[(AuPPh_3)_3O]BF_4$	35	–	–
8[c]	$AuCl_3$	–	–	–
9	**6**	–	98	–
10	**7**	–	90	–
11	$[Au(IPr)Cl]/AgBF_4$	–	35	34
12	[Au(IPr)Cl]/AgOTs	–	76	23
13	$[Au(IPr)Cl]/AgSbF_6$	–	–	89
14	[Au(IPr)Cl]/AgOTf	–	–	96
15[e]	[Au(IPr)Cl]/AgOTf	–	35	53
16	[Au(IPr)(OH)]/ TfOH	–	–	68
17	[Au(IAd)Cl]/AgOTf	–	61	traces
18	[Au(I*t*Bu)Cl]/ AgOTf	–	57	traces
19[f]	[Au(IPr)Cl]/AgOTf	–	–	75

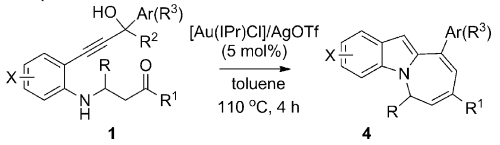
[a] All reactions were carried out under a nitrogen atmosphere. [b] Yield of isolated product after flash chromatography. [c] Decomposition of **1a** occurred. [d] Large amounts of unreacted **1a** were recovered from the reaction crude. [e] With reagent-grade toluene and under air. [f] In the presence of 2.5 mol% of catalyst. dppf = 1,1′-bis(diphenylphosphino)-ferrocene, IAd = 1,3-di(adamantyl)imidazol-2-ylidene, IPr = 1,3-di(isopropylphenyl)imidazol-2-ylidene, I*t*Bu = 1,3-di(*tert*-butyl)imidazol-2-ylidene Tf = trifluoromethanesulfonyl, Ts = *p*-toluenesulfonyl.

counterion (entries 12–14). Among these, AgOTf (Tf = trifluoromethanesulfonyl) provided **4a** in nearly quantitative yield (96%, entry 14). Gold catalysis proved essential in this transformation, as the decomposition of **1a**, along with the modest formation of **3a**, was observed to occur to a varying degree when the reaction was conducted using AgOTf or TfOH (5 mol%) in the absence of gold. The silver-free [Au(IPr)(OH)]/TfOH system (5 mol%)[15] promoted the gold-catalyzed cascade sequence in 68% yield, whereas attempts to carry out the reaction at lower temperatures or catalyst loadings led to a significant erosion in the yield of the desired product. Different N-heterocyclic carbene/gold complexes, such as [Au(IAd)Cl] (IAd = 1,3-di(adamantyl)imidazol-2-ylidene and [Au(I*t*Bu)Cl)] (I*t*Bu = 1,3-di(*tert*-butyl)imidazol-2-ylidene), were also tested, but modest results were obtained compared to those obtained with the [Au(IPr)Cl] congener (entries 17–18).

To unequivocally establish the atom connectivity present in **4a**, its structure was determined by single-crystal X-ray analysis (Table 1, scheme inset).[16]

After optimizing the reaction conditions, the generality of the method was next explored by subjecting a series of alkynyl anilines **1b–p** to the cascade ring-closing procedure. The results are summarized in Table 2. Structural modifications

Table 2: Scope of the reaction.[a]



Entry	$R/R^1/R^2$	$Ar(R^3)/X$	**4**	Yield [%][b]
1	H/Me/Me	*p*-FC_6H_4/H	**4b**	94
2	H/Me/Me	*p*-BrC_6H_4/H	**4c**	88
3	H/Me/Me	*p*-MeC_6H_4/H	**4d**	64
4	H/Me/Me	Ph/*p*-F	**4e**	93
5	H/Me/Me	*p*-FC_6H_4/*p*-F	**4f**	59
6[c]	H/Me/Me	*p*-$NO_2C_6H_4$/H	**4g**	92
7	H/Ph/Me	Ph/H	**4h**	75
8	Me/Me/Me	Ph/H	**4j**	65
9	H/Et/Me	Ph/H	**4k**	48[d]
10	H/Me/Me	*m*-MeC_6H_4/H	**4i**	78
11	H/*p*-ClC_6H_4/Me	Ph/H	**4l**	59
12	H/Me/Me	Ph/*p*-Me	**4m**	70
13[e]	H/Me/CD_3	Ph/H	[H]-**4a**	82
14	H/Me/Me	Me/H	**4n**	70
15[f]	H/Me/Me	Et/H	**4o**	55[g]
16[f]	H/Me/Me	*i*Pr/H	**4p**	50

[a] All reactions were carried out under a nitrogen atmosphere. [b] Yield of isolated product after flash chromatography. [c] Reaction time of 1 h. [d] A mixture of compounds derived from the final *endo* and *exo* dehydration event was obtained (see the Supporting Information). [e] [H]-**4a**/[D]-**4a** > 25:1 by NMR spectroscopy. [f] With 10 mol% of catalyst. [g] A 6:1 mixture of isomers was obtained (see the Supporting Information).

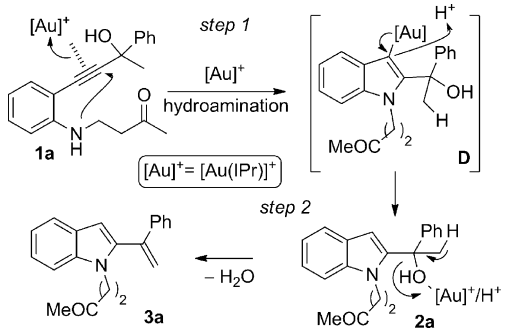
were performed at several positions on the molecule: 1) on the aniline ring, 2) on the ketone chain, and 3) on the propargylic alcohol substituents. As long as aryl tertiary alcohols were involved, the process proved to be highly selective towards substituents on the aromatic framework.[17] Electron-withdrawing substituents on the aryl groups were well tolerated and lead to the corresponding azepinoindoles **4b,c,f,g** in good yields (59–94%; Table 2, entries 1,2,5,6). Analogously, *p*-tolyl and *m*-tolyl derivatives **1d** and **1i** smoothly underwent the double ring-closing process (64–78% yield, entries 3 and 10). With regards to the aniline chain, the introduction of a methyl unit at the β-position of the ketone group did not significantly affect the reaction (**4j**, 65%, entry 8).

Analogously, substrates **1h** and **1l**, which bear an aromatic substituent on the carbonyl group (R^1 = Ph, *p*-ClC_6H_4), performed well under the optimized conditions, leading to **4h** and **4l** in 75% and 59%, respectively (entries 7 and 11). When R^1 = Et (**1k**) was employed in the reaction sequence, an inseparable mixture of azepinoindole isomers (see the Supporting Information for details) was obtained in 48%

overall yield. Finally, the introduction of electron-donating and electron-withdrawing substituents onto the aniline ring was tolerated (59-93% yield; **4e–f**,**m**) and bis(alkyl)-substituted tertiary propargylic alcohols (**1n–p**) also proved to be competent precursors, providing the corresponding tricyclic compounds **4n–p** in good yields (entries 14–16).

The present cascade sequence leads to several mechanistic questions. For example, gold(I) species could exert both π and σ acidity at different point during the reaction. Moreover, the potential for co-catalysis by the Brønsted acids formed in situ (such as TfOH when AgOTf is used) cannot be ruled out. Interestingly, the identification of compounds **2** and **3** as reaction intermediates facilitated the mechanistic investigation and allowed for the monitoring of individual reaction steps.

First, the hydroamination of the triple bond was found to proceed by gold catalysis (Scheme 2, step 1). This is supported by the unsatisfactory chemical outcomes when the reaction

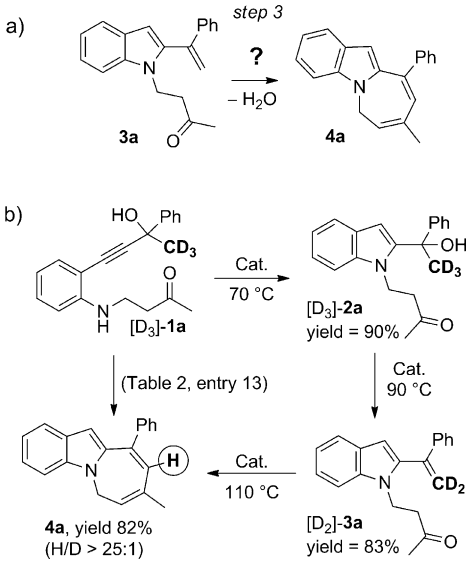


Scheme 2. Steps 1 and 2 of the [Au]-catalyzed cyclization cascade. IPr = 1,3-di(isopropylphenyl)imidazol-2-ylidene.

was carried out in the presence of AgOTf or TfOH, (entries 3–4, Table 1). At this stage, the reaction sequence could proceed through a protodeauration of the 3-[Au]-indolyl species **D** and subsequent dehydration (Scheme 2, step 2).[18,19]

Next, the condensation of 2-vinyl indole **3a** on the carbonyl unit takes place, resulting in an annulated intermediate with the formation of a seven-membered ring. A ring-closing process promoted by a Lewis acid (LA) or a Brønsted acid (Prins-type condensation) does not adequately account for the observed reactivity, as 1) treating **3a** with a catalytic amount of TfOH (5 mol% in refluxing toluene, or 15 mol% at RT) produced **4a** in only trace amounts up to 25% yield, and 2) a [Au^I]/LA-type assisted mechanism does not properly explain the unique reactivity observed with Au-NHC species when compared to more electrophilic phosphine-based gold complexes. Furthermore, the quantitative proton/deuterium exchange observed with the deuterated alcohol [D$_3$]-**1a** (Table 2, entry 13) suggested possible interactions of the vinylindole intermediate with the Au-NHC catalyst.

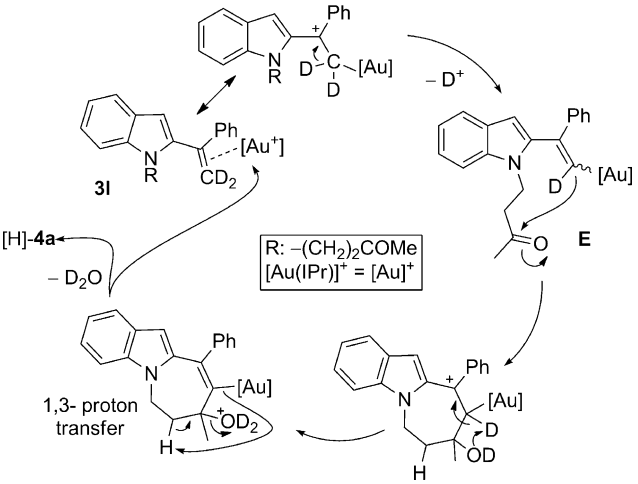
To shed light on the final reaction step of the sequence, a control experiment in the presence of [D$_3$]-**1a** was performed (Scheme 3) and the effect of varying the reaction temperature was examined for each step of the process. It was



Scheme 3. a) Step 3 of the [Au]-catalyzed cyclization cascade. b) Control experiments carried out with [D$_3$]-**1a**. Cat. = [Au(IPr)Cl]/AgOTf (5 mol%).

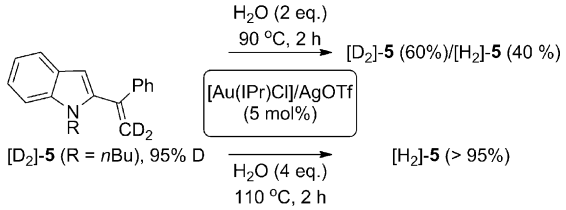
found that [Au(IPr)(OTf)] catalyzed the selective cyclizations of [D$_3$]-**1a**→[D$_3$]-**2a** and [D$_3$]-**2a**→[D$_2$]-**3a** when the reactions were conducted at 70°C and 90°C, respectively. Surprisingly, when deuterated 2-vinylindole [D$_2$]-**3a** was refluxed in toluene in the presence of [Au(IPr)(OTf)], [H]-**4a** was exclusively isolated in 82% yield and with complete proton/deuterium exchange.[20] This finding clearly suggests that a cationic Au^I/NHC species might insert into the electron-rich C=C,[14a,21,22] leading to the nucleophilic vinyl–gold species **E** (Scheme 4).[23] This would strongly suggest that the intramolecular condensation of **E** with the ketone group[24] would produce **4a** upon dehydration and 1,3-proton-transfer/protodeauration.[25]

This mechanistic rationalization was further supported by a D/H exchange observed in the control experiment carried



Scheme 4. Hypothetical C=C/[Au]$^+$ insertion leading to the formation of vinyl-gold(I) intermediate **E**.

out with *N*-butyl indole [D_2]-**5** in the presence of several equivalents of H_2O (Scheme 5). By employing [Au(IPr)Cl]/AgOTf at 110 °C with 4 equiv of water, complete conversion of [D_2]-**5** into the corresponding [H_2]-**5** was observed.



Scheme 5. C_{sp^2}–D/H exchange reaction catalyzed by [Au(IPr)Cl]/AgOTf.

In summary, an unprecedented gold-catalyzed cascade sequence has been observed for the synthesis of azepinoindoles, starting from readily available propargylic alcohols. The reaction sequence features generally high yields with water as the only stoichiometric by-product. Experimental evidence suggests the key role of vinyl–gold intermediates in the final ring-closing event.

Received: July 11, 2012
Published online: September 3, 2012

Keywords: cascade reactions · gold · homogeneous catalysis · indoles · synthetic methods

[1] P. Ertl, S. Jelfs, J. Mühlbacher, A. Schuffenhauer, P. Selzer, *J. Med. Chem.* **2006**, *49*, 4568.

[2] For a general review on the catalytic synthesis of indole rings, see: a) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873; b) K. Krüger, A. Tillack, M. Beller, *Adv. Synth. Catal.* **2008**, *350*, 2153; c) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2011**, *111*, PR215; d) R. Vicente, *Org. Biomol. Chem.* **2011**, *9*, 6469.

[3] For general reviews on the use of catalytic methods for the derivatization of indoles see: a) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608; b) S.-L. You, Q. Cai, M. Zheng, *Chem. Soc. Rev.* **2009**, *38*, 2190; c) L. Joucla, L. Djakovitch, *Adv. Synth. Catal.* **2009**, *351*, 673; d) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Chem. Soc. Rev.* **2010**, *39*, 4449; e) M. Shiri, *Chem. Rev.* **2012**, *112*, 3508.

[4] J. Barluenga, F. Rodríguez, F. J. Fañanás, *Chem. Asian J.* **2009**, *4*, 1036.

[5] For some recent leading examples using [Au], see: a) M. Alfonsi, A. Arcadi, M. Aschi, G. Bianchi, F. Marinelli, *J. Org. Chem.* **2005**, *70*, 2265; b) C. Praveen, K. Karthikeyan, P. T. Perumal, *Tetrahedron* **2009**, *65*, 9244; c) X. Zeng, R. Kinjo, B. Donnadieu, G. Bertrand, *Angew. Chem.* **2010**, *122*, 954; *Angew. Chem. Int. Ed.* **2010**, *49*, 942; d) A. Wetzel, F. Gagosz, *Angew. Chem.* **2011**, *123*, 7492; *Angew. Chem. Int. Ed.* **2011**, *50*, 7354; e) B. Lu, Y. Luo, L. Liu, L. Ye, Y. Wang, L. Zhang, *Angew. Chem.* **2011**, *123*, 8508; *Angew. Chem. Int. Ed.* **2011**, *50*, 8358; f) J. P. Brand, C. Chevalley, J. Waser, *Beilstein J. Org. Chem.* **2011**, *7*, 565; g) P. Kothandaraman, S. Reddy Mothe, S. Si Min Toh, P. W. H. Chan, *J. Org. Chem.* **2011**, *76*, 7633; for [Ag], see: h) S. R. Mothe, P. Kothandaraman, S. J. L. Lauw, S. M.-W. Chin, P. W. H. Chan, *Chem. Eur. J.* **2012**, *18*, 6133; i) for [Pd], see ref. [2d]; j) Z. Hu, D. Liang, J. Zhao, J. Huang, Q. Zhu, *Chem. Commun.* **2012**, *48*, 7371.

[6] For some representative examples, see: a) D. Bouyssi, N. Monteiro, G. Balme, *Beilstein J. Org. Chem.* **2011**, *7*, 1387, and references therein; b) Y. Oda, N. Matsuyama, K. Hirano, T. Satoh, M. Miura, *Synthesis* **2012**, 1515.

[7] For reviews on gold-catalyzed organic transformations, see: a) A. S. K. Hashmi, *Angew. Chem.* **2005**, *117*, 7150; *Angew. Chem. Int. Ed.* **2005**, *44*, 6990; b) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180; c) A. Fürstner, O. D. Davies, *Angew. Chem.* **2007**, *119*, 3478; *Angew. Chem. Int. Ed.* **2007**, *46*, 4310; d) H. C. Shen, *Tetrahedron* **2008**, *64*, 3885; e) R. Skouta, C.-J. Li, *Tetrahedron* **2008**, *64*, 4917; f) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266; g) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351; h) P. Belmont, E. Parker, *Eur. J. Org. Chem.* **2009**, 6075; i) N. D. Shapiro, F. D. Toste, *Synlett* **2010**, 675; j) S. Wang, G. Zhang, L. Zhang, *Synlett* **2010**, 692.

[8] a) M. Bandini, A. Eichholzer, M. Tragni, A. Umani-Ronchi, *Angew. Chem.* **2008**, *120*, 3282; *Angew. Chem. Int. Ed.* **2008**, *47*, 3238; b) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9697; *Angew. Chem. Int. Ed.* **2009**, *48*, 9533; c) M. Bandini, A. Gualandi, M. Monari, A. Romaniello, D. Savoia, M. Tragni, *J. Organomet. Chem.* **2011**, *696*, 338; d) M. Bandini, A. Eichholzer, A. Gualandi, T. Quinto, D. Savoia, *ChemCatChem* **2010**, *2*, 661; e) G. Cera, P. Crispino, M. Monari, M. Bandini, *Chem. Commun.* **2011**, *47*, 7803; f) G. Cera, M. Chiarucci, A. Mazzanti, M. Mancinelli, M. Bandini, *Org. Lett.* **2012**, *14*, 1350.

[9] a) L. Angenot, O. Diberg, L. Dupont, *Tetrahedron Lett.* **1975**, *16*, 1357; b) G. Massiot, P. Thépenier, M. J. Jacquier, C. Delaude, L. Le Men-Olivier, R. Verpoorte, *Tetrahedron Lett.* **1985**, *26*, 2441; c) M. Chbani, M. Païs, *J. Nat. Prod.* **1993**, *56*, 99; d) J. Kraxner, H. Hübner, P. Gmeiner, *Arch. Pharm. Pharm. Med. Chem.* **2000**, *333*, 287.

[10] a) T. W. Hudyma, X. Zheng, F. He, M. Ding, C. P. Bergstrom, P. Hewawasam, S. W. Martin, R. G. Gentles, WO2007/092000A1, **2007**; b) M. Ding, F. He, M. A. Poss, K. L. Rigat, Y.-K. Wang, S. B. Roberts, D. Qiu, R. A. Fridell, M. Gao, R. G. Gentles, *Org. Biomol. Chem.* **2011**, *9*, 6654; c) D. R. Adams, J. J. Bently, J. R. A. Roffey et al., PTC WO 00/12510A1, **2000**; d) M. D. Ennis, R. L. Hoffman, N. B. Ghazal, R. M. Olson, C. S. Knauer, C. L. Chio, D. K. Hyslop, J. E. Campbell, L. W. Fitzgerald, N. F. Nichols, K. A. Svensson, R. B. McCall, C. L. Haber, M. L. Kageyc, D. M. Dinhc, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2369.

[11] a) H. Kusama, Y. Suzuki, J. Takaya, N. Iwasawa, *Org. Lett.* **2006**, *8*, 895; b) K. Cariou, B. Ronan, S. Mignani, L. Fensterbank, M. Malacria, *Angew. Chem.* **2007**, *119*, 1913; *Angew. Chem. Int. Ed.* **2007**, *46*, 1881.

[12] For some representative examples, see: a) V. Aureggi, M. Davoust, K. M. Gericke, M. Lautens, *Synlett* **2009**, 1004; b) S. Pozzi, J. Habermann, M. de R. Rico Ferreira, F. Narjes, *Synlett* **2009**, 1395; c) P. A. Suryavanshi, V. Sridharan, J. Carlos Menéndez, *Org. Biomol. Chem.* **2010**, *8*, 3426; d) L. Huang, M. Shi, *Chem. Commun.* **2012**, *48*, 4501.

[13] J. S. Mahanty, M. De, P. Das, N. G. Kundu, *Tetrahedron* **1997**, *53*, 13397.

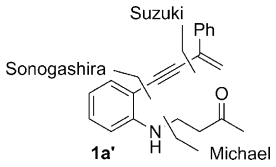
[14] For representative general reviews, see: a) N. Marion, S. P. Nolan, *Chem. Soc. Rev.* **2008**, *37*, 1776; b) J. C. Y. Lin, R. T. W. Huang, C. S. Lee, A. Bhattacharyya, W. S. Hwang, I. J. B. Lin, *Chem. Rev.* **2009**, *109*, 3561; c) S. Díez-González, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612; d) S. P. Nolan, *Acc. Chem. Res.* **2011**, *44*, 91; e) S. Gaillard, C. S. J. Cazin, S. P. Nolan, *Acc. Chem. Res.* **2012**, *45*, 778.

[15] a) S. Gaillard, J. Bosson, R. S. Ramón, P. Nun, A. M. Z. Slawin, S. P. Nolan, *Chem. Eur. J.* **2010**, *16*, 13729; b) R. S. Ramón, S. Gaillard, A. Poater, L. Cavallo, A. M. Z. Slawin, S. P. Nolan, *Chem. Eur. J.* **2011**, *17*, 1238; c) P. Nun, J. D. Egbert, M.-J. Oliva-Madrid, S. P. Nolan, *Chem. Eur. J.* **2012**, *18*, 1064.

[16] CCDC 890759 (**4a**) 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.

[17] Ene-yne compound **1a′** was considered as a possible synthetic alternative to alcohol **1a**. However, **1a′** led to extensive decomposition when subjected to the optimized reaction conditions (**4a**, 15%).



[18] A. S. K. Hashmi, T. D. Ramamurthi, F. Rominger, *Adv. Synth. Catal.* **2010**, *352*, 971.

[19] Refluxing **2a** in toluene for a few hours in the absence of acid sources led to the quantitative recovery of unreacted alcohol.

[20] When [D_2]-**3a** was reacted in the presence of TfOH (5 mol%) at RT, [D]-**4a** was isolated in 25%, whereas refluxing conditions led to decomposition of the starting material.

[21] a) T. J. Brown, M. G. Dickens, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2009**, *131*, 6350; b) T. J. Brown, M. G. Dickens, R. A. Widenhoefer, *Chem. Commun.* **2009**, 6451; c) D. Zuccaccia, L. Belpassi, F. Tarantelli, A. Macchioni, *J. Am. Chem. Soc.* **2009**, *131*, 3170; d) N. Salvi, L. Belpassi, D. Zuccaccia, F. Tarantelli, A. Macchioni, *J. Organomet. Chem.* **2010**, *695*, 2679. See also: M. A. Cinellu in *Modern Gold Catalyzed Synthesis* (Eds.: A. S. K. Hashmi, F. D. Toste), Wiley-VCH, Weinheim, **2012**, chap. 7, p. 175, and references therein.

[22] For representative examples of the gold(I)-catalyzed isomerization of C=C and corresponding H/D exchange, see: a) C.-G. Yang, C. He, *J. Am. Chem. Soc.* **2005**, *127*, 6966; b) A. R. Jagdale, J. H. Park, S. W. Youn, *J. Org. Chem.* **2011**, *76*, 7204.

[23] For general reviews and reports on the isolation of organogold intermediates, see: a) A. S. K. Hashmi, A. M. Schuster, F. Rominger, *Angew. Chem.* **2009**, *121*, 8396; *Angew. Chem. Int. Ed.* **2009**, *48*, 8247; b) L.-P. Liu, G. B. Hammond, *Chem. Soc. Rev.* **2012**, *41*, 3129; c) D. Weber, M. A. Tarselli, M. R. Gagné, *Angew. Chem.* **2009**, *121*, 5843; *Angew. Chem. Int. Ed.* **2009**, *48*, 5733.

[24] a) M. Zhang, Y. Wang, Y. Yang, X. Hu, *Adv. Synth. Catal.* **2012**, *354*, 981.

[25] The in situ formation of a nucleophilic 3-gold-indolyl derivative seems unlikely, as [Au(IPr)Cl]-assisted aromatic C–H activation was observed only for electron-deficient arenes ($pK_a \leq 31$) and in the presence of Ag_2O; see: P. Lu, T. C. Boorman, A. M. Z. Slawin, I. Larrosa, *J. Am. Chem. Soc.* **2010**, *132*, 5580, and ref. [14d] for discussion. Moreover, when H_2-**5** was treated with [Au(IPr)(OTf)] ([D_8]-toluene, reflux) activation of the C3–H position of the indole core was not observed by NMR spectroscopy.

