CHEMISTRY
AN ASIAN JOURNAL
ACES
COMMUNICATION

DOI: 10.1002/asia.201201249

# New Entry to Polycyclic Fused Indoles via Gold(I)-catalyzed Cascade Reaction

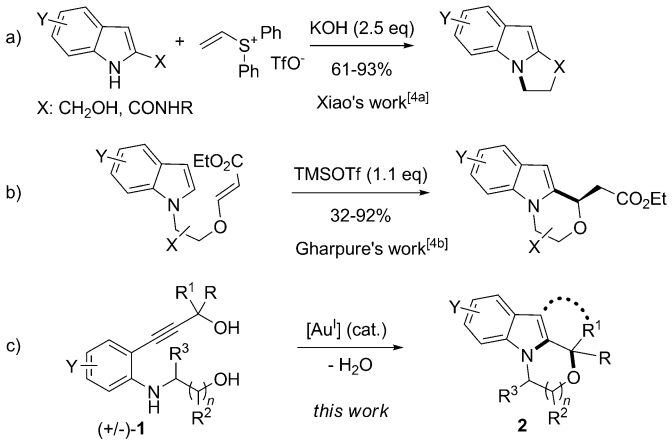
**Michel Chiarucci,[a] Elia Matteucci,[a] Gianpiero Cera,[a] Giancarlo Fabrizi,[b] and Marco Bandini*[a]**

Polycyclic indoles are pivotal motifs in naturally occurring compounds, featuring a plethora of pharmacological and agrochemical applications.[1] Large chemical decoration and nontrivial molecular scaffolds are common architectural patterns in indole-based alkaloids that still trigger organic chemists in developing chemically and economically efficient and sustainable methodologies for their preparation. Accordingly, efforts towards the synthesis of indole derivatives by means of metal as well as metal-free catalysis are growing exponentially.[2]

In this realm, N-fused indole alkaloids based on oxazino-[4,3-*a*]indole and pyrazino[1,2-*a*]indole platforms have attracted growing attention due to their peculiar activity as ligands for 5-$HT_{2C}$ receptor, antidepressant, and 5-$HT_4$ receptor antagonists.[3]

Very recently, the synthesis of densely functionalized oxazinoindoles has been addressed independently by the groups of Xiao[4a] and Gharpure[4b] through the N(1) or C(2) alkylation of the indole core with vinyl sulfonium salts and via Michael addition, respectively. Both of these elegant approaches required stoichiometric amounts of Lewis acid (i.e., $(CH_3)_3SiOTf$) or base (i.e., KOH) along with the preformed indole nucleus, with inevitable repercussions on the availability of the acyclic precursors (Scheme 1 a, b).

We recently entered a new scientific program addressing the simultaneous synthesis and functionalization of indole cores assisted by the same catalytic species.[5] In particular, we documented the combined use of π-activated alcohols[6] (i.e., propargylic alcohols) and gold catalysis[7] as a powerful tool towards this goal. Tertiary propargylic alcohols,[8] when allowed to react in the presence of mild metal bifunctional π/σ acids,[9] can act as electrophiles towards the C–C triple bond, and the alcoholic group can exert either nucleophilic or electrophilic character, depending on the chemical surrounding.[8] Based on this chemical flexibility, we envisioned an unprecedented synthesis of densely functionalized tricyclic oxazino[4,3-*a*]indoles **2** by means of simultaneous construction of the indole and the N(1)-C(2)-fused ring, starting from readily available aniline diols **1**. The mechanistic plan would involve a cascade hydroamination/dehydrative synthetic sequence, delivering water as the only stoichiometric by-product of the entire process (Scheme 1 c).




Scheme 1. a, b) State of the art in the synthesis azepino[4,3-*a*]indoles. c) Synthetic approach of this work.

The choice of unprotected amine diol **1** as model substrate significantly restricted the class of potentially useful promoting agents. While Brønsted acids would presumably form the unreactive corresponding ammonium salts, conventional σ Lewis acids could either be irreversibly deactivated by coordination to the hard heteroatoms or would lead to decomposition of the starting material if propargylic carbocations are formed before the hydroamination of the C–C triple bond takes place. Consequently, π acid late-transition-metal species appeared to be the promoters of choice for the titled transformation.

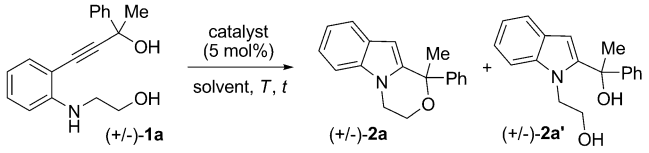
In Table 1, we summarize some of the results obtained during the optimization of the catalytic system, choosing **1a** as the model substrate. As expected, organic Brønsted acids such as $HNTf_2$ and *p*TsOH were not efficient, leading to rapid decomposition of **1a** (Table 1, entries 1,2). Similar chemical outcomes were recorded with $In(OTf)_3$ (Table 1,

[a] Dr. M. Chiarucci, E. Matteucci, G. Cera, Prof. M. Bandini
Department of Chemistry "G. Ciamician", Alma Mater Studiorum—University of Bologna
via Selmi 2, 40138 Bologna (Italy)
Fax: (+39) 051-2099456
E-mail: marco.bandini@unibo.it

[b] Prof. G. Fabrizi
Dipartimento di Chimica e Tecnologia del Farmaco
Sapienza, Università di Roma
P.le A. Moro, 5, Rome (Italy)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201201249.

Table 1. Optimization of the catalytic system for the cascade synthesis of oxazino[4,3-*a*]indole **2a**.[a]




| Entry | Catalyst | $T$ [°C]/$t$ [h] | Yield **2a**/**2a′** [%][b] |
|---|---|---|---|
| 1[c] | $HNTf_2$ | 25/3.5 | –/– |
| 2[c] | *p*TsOH | 25/3.5 | –/– |
| 3[c] | $AgNTf_2$ | 25/3.5 | 9/– |
| 4[c] | $In(OTf)_3$ | 25/3.5 | –/– |
| 5[d] | $[(PPh_3)_2PdCl_2]$ | 25/3.5 | –/– |
| 6 | $AuCl_3$/AgOTf | 25/3.5 | 16/– |
| 7[d] | $[PPh_3AuNTf_2]$ | 25/3.5 | –/11 |
| 8 | [JhonPhosAu]$(SbF_6)(CH_3CN)$ | 25/17.5 | –/57 |
| 9 | [AuIPrCl]/$AgNTf_2$ | 25/3.5 | 55/– |
| 10 | $[XPhosAuNTf_2]$ | 25/3.5 | 71/– |
| 11[e] | [XPhosAuCl]/AgOTf | 25/3.5 | 62/– |
| 12[e] | [XPhosAuCl]/AgOTs | 25/3.5 | 33/– |
| 13[e] | [XPhosAuCl]/$AgSbF_6$ | 25/3.5 | –/24 |
| 14[e] | [XPhosAuCl]/$AgBF_4$ | 25/3.5 | –/25 |
| 15 | $[XPhosAuNTf_2]$ | 50/3.5 | 92/– |
| 16[f] | $[XPhosAuNTf_2]$ | 50/48 | 76/– |

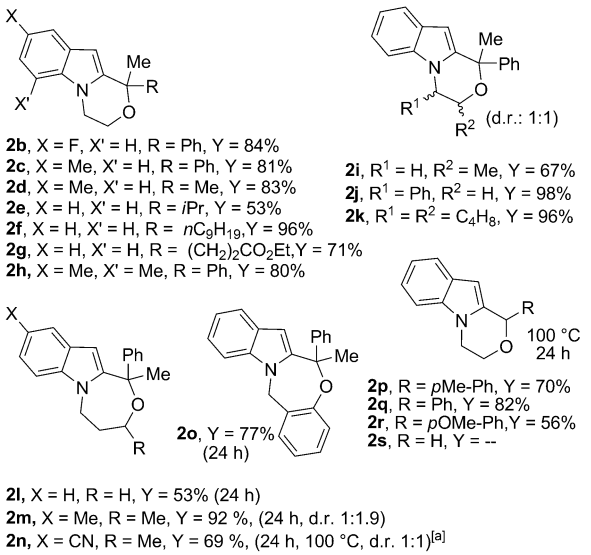
[a] All the reactions were carried out under nitrogen atmosphere in anhydrous toluene with 5 mol% loading of catalyst, unless otherwise specified. [b] Yields of produce isolated after flash chromatography. [c] Substantial decomposition of **1a** was observed. [d] Starting material **1a** was recovered untouched. [e] XPhosAuCl was formed in situ. [f] With 1 mol% of $XPhosAuNTf_2$. Tf = $CF_3SO_2$, Ts = *p*-$CH_3C_6H_4SO_2$, JhonPhos = (2-biphenyl)di-*tert*-butylphosphine, XPhos = dicyclohexyl[2′,4′,6′-tris(1-methylethyl)[1,1′-biphenyl]-2-yl]phosphine, IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene.

entry 4), while $AgNTf_2$ furnished **2a** but in unsatisfactory manner (yield = 9%, Table 1, entry 3).

Some improvements were recorded in the presence of $AuCl_3$/AgOTf (5 mol%), which led to **2a** in 16% yield along with the recovery of untouched **1a** (Table 1, entry 6). This finding prompted us to investigate less heterophilic [$Au^I$] species, and the results are listed in Table 1, entries 7–16. Well-defined silver-free Gagosh complex $[PPh_3AuNTf_2]$[10] and [JhonPhosAu]$(SbF_6)(CH_3CN)$[11] showed some aptitude in triggering the initial *5-endo-dig* cyclization (**2a′**, 11% and 57%, respectively), but the second ring-closing event was not promoted at all (Table 1, entries 7,8). To our delight, cationic gold carbene species [AuIPrCl]/$AgNTf_2$[12] and commercially available $[XPhosAuNTf_2]$[13] provided **2a** in 55% and 71% yield, respectively, at room temperature after 3.5 h reaction time (Table 1, entries 9,10).

The role of the counterion was then investigated, and control experiments (Table 1, entries 11–14) clearly show the superior efficiency of $NTf_2$ in comparison to OTf, OTs, and $SbF_6$.[14] Finally, we were pleased that the reaction at 50°C in the presence of silver-free $[XPhosAuNTf_2]$ (5 mol%) gave quantitative conversion within 3.5 h, providing **2a** in 92% yield (Table 1, entry 15). The loading of the catalyst was also reduced to 1 mol%; in this case longer reaction time was required (48 h) but synthetically useful yield (76%) was still obtained (Table 1, entry 16).

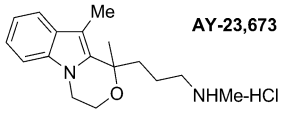
Having established the optimal reaction conditions, we examined the generality of the methodology in terms of substrate scope. A range of tertiary and secondary propargylic alcohols (**1b–s**) were synthesized and subjected to the double ring-closing process under the assistance of $[XPhosAuNTf_2]$ (5 mol%, toluene, 50°C). A collection of tricyclic and tetracyclic products is summarized in Scheme 2.




Scheme 2. Scope of the reaction (reaction conditions: $XPhosAuNTf_2$ (5 mol%), toluene, 50°C, 3.5 h, unless otherwise specified). All substrates were obtained as racemic mixtures. [a]: IPrAuCl/$AgNTf_2$ (5 mol%) as the catalyst.

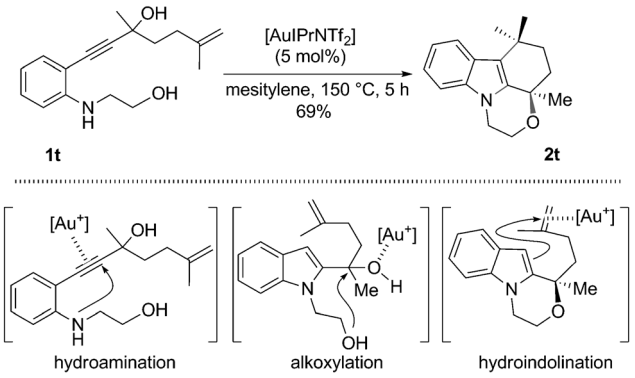
A range of oxazinoindoles (**2b–h**) were obtained in good to excellent yields (53–96%). In particular, aliphatic (**2d–g**) and aromatic groups (**2b**,**c**,**h**,) on the carbynol carbon atom were adequately tolerated along with electron-withdrawing and electron-donating groups on the aniline ring. Moreover, the oxazinyl ring was also substituted with aryl and alkyl groups, leading to compounds **2i–k** in good yields (67–98%).

Remarkably, the methodology was efficiently applied to the levulinate derivative **1g** that led to the key precursor of antidepressant **AY-23,673** in 71% yield (100°C, 3.5 h).[15] Important building blocks in medical chemistry such as tetrahydro-[1,4]oxazepino[4,3-*a*]indoles,[16] featuring a seven-membered ring fused at the N(1)/C(2) positions (**2l–o**), were also accessible through the present protocol in good yield (53–92%).

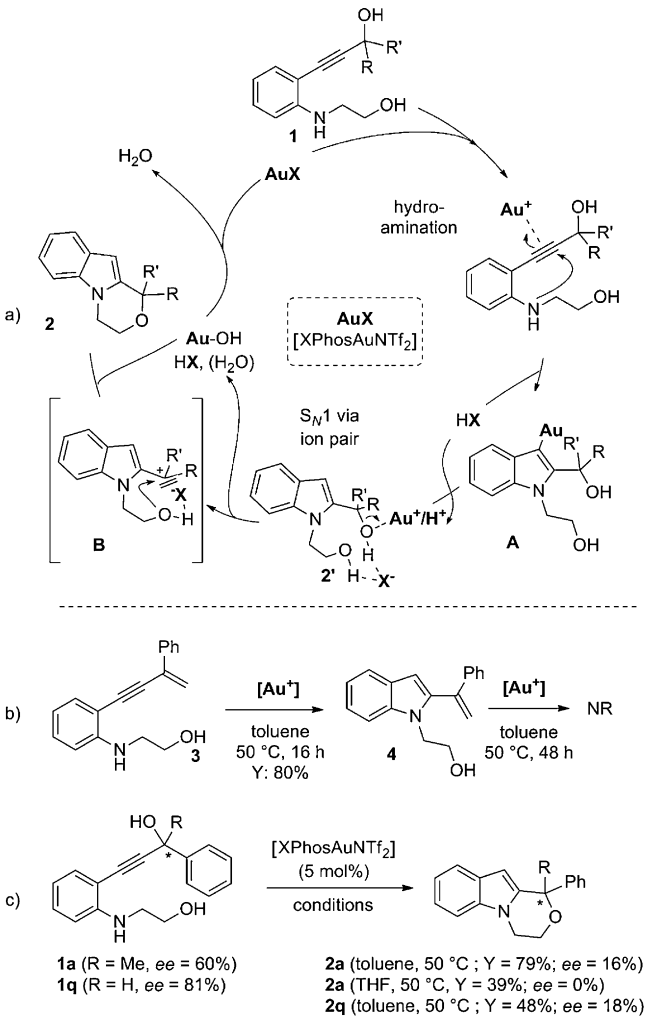


Finally, we explored the gold-catalyzed cascade reaction with secondary propargylic alcohols. Despite the higher reaction temperature required (100 °C), the corresponding targeted compounds **2p–r** were obtained in reasonable yields (56–82 %). On the contrary, primary propargylic alcohol **1s** was recovered untouched, thus suggesting that ionic species are involved in the final C–O bond-forming event of the catalytic cycle (see below).

The synthetic potential of the present methodology was underlined further by the realization of a triple-cascade reaction using **1t** as starting material. The use of 5 mol % [AuIPrNTf$_2$] led to the one-pot regioselective *5-endo-dig* hydroamination of the C–C triple bond, alkoxylation of the carbynol carbon atom, and *6-exo-trig* hydroindolination of the olefin in satisfying yield (69 %, Scheme 3). The three consecutive gold-assisted ring-closing events (i.e., hydroamination, alkoxylation, hydroindolination) open an efficient access to tetracyclic indolyl scaffolds of type **2t**, featuring concomitant N(1), C(2) and C(3) functionalization.




Scheme 3. Triple cascade reaction promoted by gold.




Scheme 4. a) Tentative reaction mechanism for the [Au$^I$]-catalyzed cascade reaction. b,c) Control experiments that support the S$_N$1 mechanism via intimate ion pairs. NR = no reaction.

Scheme 4a shows a tentative reaction mechanism. In particular, after the initial regioselective gold-triggered formation of the indolyl core (*5-endo-dig* hydroamination of the triple bond), protodeauration of the resulting indolyl-3-Au intermediate **A**[16] would lead to intermediate **2′**. In support of this pathway, indolyl diol **2′** was isolated in some cases from the crude reaction mixtures as a minor compound, and when treated in toluene in the presence of freshly added [XPhosAuNTf$_2$] (5 mol %), the corresponding tricyclic compound **2a** was isolated in quantitative yield. At this stage, several mechanistic channels could be hypothesized.

In particular, dehydration and consequent oxyalkylation of the olefin can be excluded due to the thermodynamically unfavorable dehydration of C2-indole tertiary alcohols at 50 °C. Moreover, when the probe ene-ino compound **3** was subjected to gold catalysis, only partially cyclized 2-vinyl indole **4** was isolated in 80 % yield (Scheme 4b) Interestingly, compound **4** was recovered untouched even after prolonged reaction (48 h), thus demonstrating the unfeasibility of the gold-catalyzed hydroalkoxylation of the electron-rich carbon–carbon double bond.

To more thoroughly investigate the second cyclization event, enantiomerically enriched alcohols **1a** (*ee* = 60 %) and **1q** (*ee* = 81 %, see the Supporting Information) were allowed to react in the presence of [XPhosAuNTf$_2$] (5 mol %). Unexpectedly, under optimal conditions (i.e., toluene, 50 °C), significant but not complete racemization was recorded in both cases (Scheme 4c).[17,18] This evidence can be rationalized with a "not-pure" S$_N$1-type mechanism[19] in the presence of ion pairs of type **B**. Accordingly, we recently reported on the "folding effect" played by the counterion in the enantioselective gold-catalyzed alkylation of indoles with allylic alcohols.[20] Here, the negatively charged species (i.e., OTf$^-$) binds simultaneously to the acidic protons of the substrate. Analogous situation could be envisioned in the present C–O bond-forming process (see intermediate **2′**), with direct impact of the gold counterion on the geometry of the incoming electrophilic center.[21]

To confirm the presence of ion pairing in the C–O bond-forming event, a highly coordinating solvent (i.e., THF) was

utilized, leading to the desired product in lower yield (39%) and to complete racemization. This speculative interpretation is also in agreement with the decreasing reactivity trend recorded with the propargylic alcohols (tertiary > secondary > primary) that also tends to exclude a mixed $S_N1$–$S_N2$ reaction profile.[22]

In conclusion, an unprecedented gold-catalyzed cascade reaction sequence for the preparation of polycyclic fused indole cores is reported. The methodology exploits the ready availability and chemical flexibility of propargylic alcohols, leading to the desired tri- or tetracyclic compounds in good yields and delivering water as the only stoichiometric by-product. Efforts towards the realization of an enantioselective variant of the protocol are currently underway and will be presented in due course.

## Acknowledgements

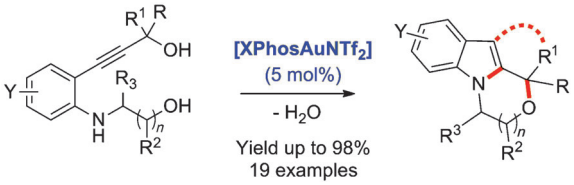
Acknowledgements is made to Progetto FIRB "Futuro in Ricerca" *Innovative sustainable synthetic methodologies for C–H activation processes*, (MIUR, Rome) and Università di Bologna.

**Keywords:** domino reactions · heterocycles · homogeneous catalysis · gold

[1] a) W. G. Sumpter, F. M. Miller in *Natural Products Containing Indole*, Wiley, New York, **2008**, chap. VIII.
[2] Synthesis of indoles: a) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873–2920; b) K. Krüger, 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; d) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2011**, *111*, PR215–PR283; e) R. Vicente, *Org. Biomol. Chem.* **2011**, *9*, 6469–6480; functionalization: f) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786–9824; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644; g) S.-L. You, Q. Cai, M. Zheng, *Chem. Soc. Rev.* **2009**, *38*, 2190–2201; h) L. Joucla, L. Djakovitch, *Adv. Synth. Catal.* **2009**, *351*, 673–714; i) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Chem. Soc. Rev.* **2010**, *39*, 4449–4465; j) M. Shiri, *Chem. Rev.* **2012**, *112*, 3508–3549.
[3] a) C. A. Demerson, G. Santroch, L. G. Humber, *J. Med. Chem.* **1975**, *18*, 577–580; b) C. Farina, S. Gagliardi, P. Misiano, P. Celestini, F. Zunino, PCT Int. Appl., WO 2005105213A2 20051110, **2005**.
[4] a) J. An, N.-J. Chang, L.-D. Song, Y.-Q. Jin, Y. Ma, J.-R. Chen, W.-J. Xiao, *Chem. Commun.* **2011**, *47*, 1869–1871; b) S. J. Gharpure, A. M. Sathiyanarayanan, *Chem. Commun.* **2011**, *47*, 3625–3627.
[5] G. Cera, S. Piscitelli, M. Chiarucci, G. Fabrizi, A. Goggiamani, R. S. Ramón, S. P. Nolan, M. Bandini, *Angew. Chem.* **2012**, *124*, 10029–10033; *Angew. Chem. Int. Ed.* **2012**, *51*, 9891–9895.
[6] Fore recent reviews on the use of π alcohols in organic synthesis, see: a) J. Muzart, *Tetrahedron* **2005**, *61*, 4179–4212; b) Y. Tamaru, *Eur. J. Org. Chem.* **2005**, 2647–2656; c) J. Muzart, *Eur. J. Org. Chem.* **2007**, 3077–3089; d) M. Bandini, M. Tragni, *Org. Biomol. Chem.* **2009**, *7*, 1501–1507; e) E. Emer, R. Sinisi, M. G. Capdevila, D. Petruzziello, F. D. Vincentiis, P. G. Cozzi, *Eur. J. Org. Chem.* **2011**, 647–666; f) B. Biannic, A. Aponick, *Eur. J. Org. Chem.* **2011**, 6605–6617; g) M. Bandini, G. Cera, M. Chiarucci, *Synthesis* **2012**, 504–512.
[7] For recent monographs and reviews of the use of gold complexes in homogeneous catalysis, see: a) *Modern Gold Catalyzed Synthesis* (Eds.: A. S. K. Hashmi, F. D. Toste), Wiley-VCH, Weinheim, **2012**; b) *Gold Catalysis: An Homogeneous Approach* (Eds.: F. D. Toste, V. Michelet), Imperial College Press, London, **2012**; c) M. Rudolph, A. S. K. Hashmi, *Chem. Soc. Rev.* **2012**, *41*, 2448–2462; d) T. de Haro, C. Nevado, *Synthesis* **2011**, 2530–2539; e) M. Bandini, *Chem. Soc. Rev.* **2011**, *40*, 1358–1367.
[8] E. B. Bauer, *Synthesis* **2012**, 1131–1151.
[9] Y. Yamamoto, *J. Org. Chem.* **2007**, *72*, 7817–7831.
[10] N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133–4136.
[11] a) C. Nieto-Oberhuber, S. Lòpez, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179; b) E. Herrero-Gómez, C. N. Oberhuber, S. López, J. Benet-Buchholz, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 5581–5585; *Angew. Chem. Int. Ed.* **2006**, *45*, 5455–5459.
[12] a) N. Marion, S. P. Nolan, *Chem. Soc. Rev.* **2008**, *37*, 1776–1782; b) S. Díez-González, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612–3672; c) S. P. Nolan, *Acc. Chem. Res.* **2011**, *44*, 91–100; d) S. Gaillard, C. S. J. Cazin, S. P. Nolan, *Acc. Chem. Res.* **2012**, *45*, 778–787.
[13] G. C. Fortman, S. P. Nolan, *Organometallics* **2010**, *29*, 4579–4583.
[14] For recent studies on the role of counterions in gold(I)-catalyzed organic transformations, see: a) H. Schmidbaur, A. Schier, *Z. Naturforsch. B* **2011**, *66*, 0329–0350; b) D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen, X. Shi, *J. Am. Chem. Soc.* **2012**, *134*, 9012–9019.
[15] 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*, 6654–6662, and references cited therein.
[16] A. S. K. Hashmi, T. D. Ramamurthi, F. Rominger, *Adv. Synth. Catal.* **2010**, *352*, 971–975.
[17] For a recent review on gold-catalyzed chiral transfer and memory effects, see: N. T. Patil, *Chem. Asian J.* **2012**, *7*, 2186–2194.
[18] At the present it is not possible to discriminate between partial inversion or retention of configuration.
[19] a) I. P. Beletskaya, *Russ. Chem. Rev.* **1975**, *44*, 1067–1090; b) J. M. Harris, *Prog. Phys. Org. Chem.* **1974**, *11*, 89–173; c) D. J. Raber, J. M. Harris, P. v. R. Schleyer in *Ions and Ion Pairs in Organic Reactions*, *Vol. 2* (Ed.: M. Szwarc), Wiley, New York, **1974**, pp. 247–374.
[20] M. Bandini, A. Bottoni, M. Chiarucci, G. Cera, G. Miscione, *J. Am. Chem. Soc.* **2012**, *134*, 20690–20700.
[21] a) D. Zuccaccia, L. Belpassi, F. Tarantelli, A. Macchioni, *J. Am. Chem. Soc.* **2009**, *131*, 3170–3171; b) N. Salvi, L. Belpassi, D. Zuccaccia, F. Tarantelli, A. Macchioni, *J. Organomet. Chem.* **2010**, *695*, 2679–2686.
[22] R. A. Sneen, *Acc. Chem. Res.* **1973**, *6*, 46–53.

Received: December 30, 2012
Published online: ■■ ■■, 0000

# COMMUNICATION




**The gold standard**: A gold-catalyzed cascade reaction sequence for the preparation of polycyclic fused indole cores exploits the ready availability and chemical flexibility of propargylic alcohols. The desired tri- or tetracyclic compounds are obtained in good yields with water as the only stoichiometric by-product.

**Domino Reactions**

*Michel Chiarucci, Elia Matteucci, Gianpiero Cera, Giancarlo Fabrizi, Marco Bandini** _____ ▮▮▮▮–▮▮▮▮

**New Entry to Polycyclic Fused Indoles via Gold(I)-catalyzed Cascade Reaction**