ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 7803–7805

www.rsc.org/chemcomm

COMMUNICATION

Stereoselective synthesis of tetracyclic indolines *via* gold-catalyzed cascade cyclization reactions†

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Received 21st April 2011, Accepted 10th May 2011
DOI: 10.1039/c1cc12328a

A reliable synthetic route to fused polycyclic indolines is documented by the development of a stereoselective gold catalyzed cascade cyclization of indole propargylic alcohols.

Indoline alkaloids are prominent molecular motifs in naturally occurring compounds displaying distinct pharmacological properties.[1] These compounds are commonly constituted by polycyclic fused molecular architectures featuring quaternary stereocenters,[2] and represent stimulating/nontrivial synthetic exercises for organic chemists. Although cascade methodologies are rising to prominence,[3] elaborate multi-step synthetic sequences are still normally required for the preparation of stereochemically defined indoline alkaloids.[4] As a consequence, it is not surprising to record a growing need for selective and sustainable procedures for the preparation of densely functionalized polycyclic indolines.

In relation to our recent interests in the stereoselective gold catalyzed functionalization of indole cores,[5,6] we reasoned that the functional group compatibility and fine-tunability, commonly associated with gold catalyzed transformations of unsaturated hydrocarbons,[7] would constitute desirable requirements to implement atom/step economical synthetic shortcuts to structurally complex indoline alkaloids.

The present working hypothesis relied on the use of readily available unprotected (NH)-indole propargylic alcohols **A** that when subjected to electrophilic activation of the C–C triple bond by gold species[8] could enter into a Friedel–Crafts alkylation/iminium trapping reactive sequence (Fig. 1).[9] A main strength of the methodology relies on the widely accessible chemical diversity (*i.e.* tetracyclic dihydropyranylindolines **B** and corresponding furoindolines **C**),[10] due to the interplay of structural design of the acyclic precursor (n = 1,2) with the high regioselectivity featured by the gold assisted hydroindolination of alkynes.[11,12]

At the outset of the investigation, we identified in the unprotected (NH)-indole alcohol **1a**, a readily accessible model substrate comprising the molecular requisites exemplified by compound **A**. A survey of reaction conditions namely: gold source, solvent and temperature was then undertaken and the results are collected in Table 1.

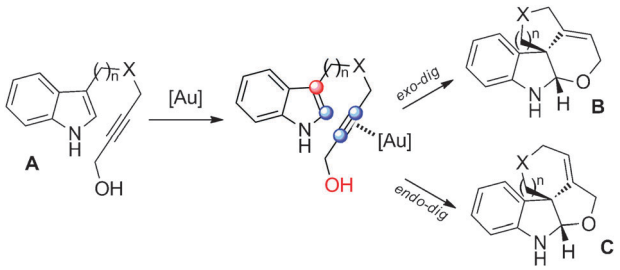

Fig. 1 Working plan for the synthesis of polycyclic fused indolines (in red nucleophilic sites, in blue electrophilic sites).

Early screening experiments with different gold sources revealed that cationic gold(I) catalysts displayed greater competence with respect to [Au(III)] analogues (entries 1 and 2), in providing the tetracyclic fused indoline **2a** (yields up to 33%). This trend can be tentatively ascribed to poisoning phenomena exerted by the aminic nitrogen atom of **2a** on the most electrophilic [Au(III)] species. Among the gold(I) π-acids scrutinized (entries 3–7), the well-defined silver-free complex **3b** (5 mol%)[13] was elected as the catalyst of choice providing **2a** with high 5-*exo-dig* regiochemistry (*vide infra* for X-ray analysis) and an excellent diastereomeric ratio (yield = 74%, dr > 50 : 1, entry 7). Among the solvents examined (MeOH, toluene, $MeNO_2$ and DCM, entries 7–10), CH_2Cl_2 proved to be the reaction media of choice. Moreover, partial decomposition of the starting compound was recorded under forced conditions (toluene, reflux, entry 11) and higher loadings of **3b** (*i.e.* 10 mol%) did not significantly impact the isolated yield of **2a** (80%, entry 12, Table 1). Then, the roles of the counterion as well as the phosphine ligand were further investigated through experimental controls carried out with preformed gold complexes [PPh_3AuCl] and [dppf$(AuCl)_2$] in the presence of $AgSbF_6$ (entries 13 and 14). Here, while the entry 13 proved unambiguously the superiority of SbF_6 with respect to OTf counterion in terms of chemical yield (entry 13 *vs.* 3), dinuclear cationic gold species [dppf$(AuSbF_6)_2$] led to **2a** in lower extent (yield = 31%). Finally, it is worth noting that, at a difference with the recent report by Wang and coworkers,[9] the presence of activating EWG groups on the N(1)-atom was not mandatory in our methodology.

The substrate scope was then ascertained by subjecting a range of indole propargylic alcohols (**1b–j**) to the cascade

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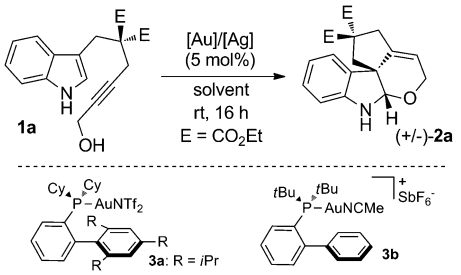
† Electronic supplementary information (ESI) available: CCDC 814206 (**2c**) and 814207 (**5a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc12328a

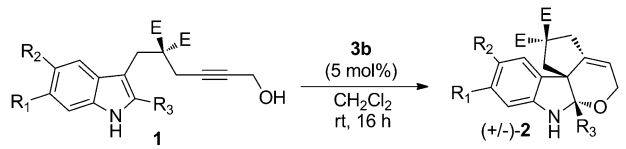
Table 1 Catalyst optimization for the gold catalyzed tandem cyclization of **1a**[a]



Entry	[Au]	[Ag]	Solvent	Yield[b] (%)
1	$AuCl_3$	—	Toluene	10
2	$AuCl_3$	AgOTf	Toluene	33
3	$[PPh_3AuCl]$	AgOTf	CH_2Cl_2	45
4	$[(PPh_3Au)_3O]BF_4$	—	CH_2Cl_2	72
5	[AuIMes]Cl	AgOTf	CH_2Cl_2	55
6	**3a**	—	CH_2Cl_2	60
7	**3b**	—	CH_2Cl_2	74
8	**3b**	—	Toluene	72
9	**3b**	—	MeOH	61
10	**3b**	—	$MeNO_2$	63
11[c]	**3b**	—	Toluene	56
12[d]	**3b**	—	CH_2Cl_2	80
13	$[PPh_3AuCl]$	$AgSbF_6$	CH_2Cl_2	68
14	$[dppf(AuCl)_2]$	$AgSbF_6$	CH_2Cl_2	31

[a] All the reactions were carried out under nitrogen conditions at room temperature, unless otherwise specified. [b] Isolated yield after flash chromatography. In all cases, compound **2a** was obtained as a single diastereoisomer (^{1}H-NMR and LC-analysis). [c] Under reflux. [d] 10 mol% of the catalyst was used at rt. IMes = 1,3-bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene.

Table 2 Scope of the diastereoselective gold catalyzed synthesis of indolines **2**[a]



Entry	$R_1/R_2/R_3$	E	Solvent	Yield[b] (%)
1	H/H/H (**1b**)	CO_2Me	**2b**	75
2	H/H/H (**1c**)	CO_2tBu	**2c**	70
3	H/H/H (**1c**)	CO_2tBu	**2c**	81[c]
4	H/Me/H (**1d**)	CO_2Et	**2d**	70[c]
5	H/OMe/H (**1e**)	CO_2Et	**2e**	86[c]
6	H/Cl/H (**1f**)	CO_2Me	**2f**	75
7	H/Cl/H (**1g**)	CO_2Et	**2g**	75
8	H/Br/H (**1h**)	CO_2Et	**2h**	75
9	Cl/H/H (**1i**)	CO_2Et	**2i**	78
10	H/H/Me (**1j**)	CO_2Et	**2j**	59

[a] All the reactions were carried out under nitrogen conditions at room temperature. [b] Isolated yield after flash chromatography. In all cases, compounds **2** were isolated as a single diastereoisomer (^{1}H-NMR and LC-analysis). [c] In the presence of 10 mol% of the catalyst.

ring-closing reaction under the most favourable experimental conditions (Table 2). Firstly, the malonyl tethering unit did not exhibit a marked influence on the final chemical output, and the corresponding dihydropyranyl indolines **2b**,**c** were isolated in comparable yields (70–81%, entries 1–3). Good yields (up to 78%) were also obtained in the presence of electron-withdrawing groups located at the C(5)- and C(6)-positions of the indolyl ring (entries 6–9).

Contrarily, indole compounds carrying electron-donating groups (*i.e.* **1d**,**e**) proved to be more reluctant toward the cascade cyclization, however by increasing the catalyst loading to 10 mol%, indolines **2d**,**e** were isolated in high chemical yields (70–86%, entries 4 and 5). Moreover, also 2-methylindole derivative **1j** proved to be a suitable precursor for compound **2j**, with the simultaneous formation of two consecutive quaternary stereocenters in a diastereomerically defined manner (yield = 59%, entry 10).

Subsequently, the scope of the synthetic method was expanded further, by highlighting its compatibility to indolyl precursors **4a–d**, derived from the corresponding tryptamine derivatives.

It is worth noting that, by subjecting these alcohols to optimal ring-closing conditions (**3b**, CH_2Cl_2, rt, 16 h) tetracyclic polyfunctionalized furoindolines **5a–d** (7-*endo-dig* pathway) were isolated in moderate to good yields (52–76%) as single diastereoisomers (Fig. 2). Also in this case, both EWGs and EDGs were efficiently supported by the gold catalysis. Interestingly, opposite regiochemistry, with respect to alcohols **1** was recorded. This inversion can be tentatively rationalized in terms of intrinsic molecular requisites of the precursors. As a matter of fact, while the 6-*endo-dig* mechanism seems not structurally accessible for compounds **1**-type, due to the limited length of the side chain, the introduction of longer and more flexible side arms (*i.e.* compounds **4**)[14] opens access to the 7-*endo-dig* cyclization pathway, as previously reported in the hydroindolination of unfunctionalized internal alkynes.[11b]

The molecular architectures of dihydropyranyl indolines and *N*Ts-furoindolines were unambiguously determined by single crystal X-ray diffraction studies on compounds **2c** and **5a** (Fig. 3).

Mechanistically, although detailed experimental evidences are still elusive, a tentative hypothesis is depicted in Scheme 1. Here, the initial Au(I)-assisted electrophilic activation of the triple bond can trigger a Friedel–Crafts-type alkylation of the indole ring, with the formation of spirovinyl-gold intermediates **D**.[15,16] Then, the regioselective functionalization of the C(3)-position of the indole nucleus could provide an avenue toward the trapping of the incipient iminium group by the hydroxyl group. Finally, the protodeauration step would result into the desired tetracyclic compounds **2** or **5**.[17]

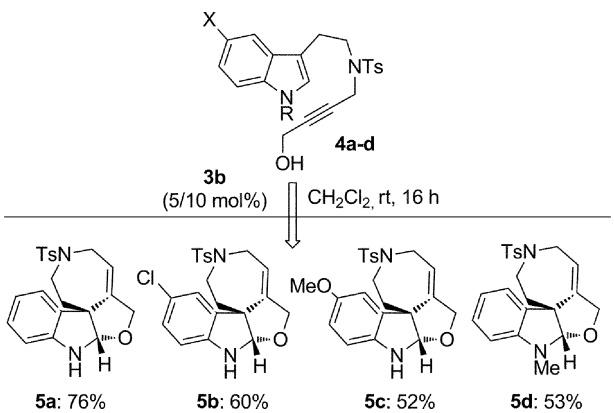


Fig. 2 Tetracyclic furoindolines derived from *N*Ts tryptamine precursors **4a–d**.

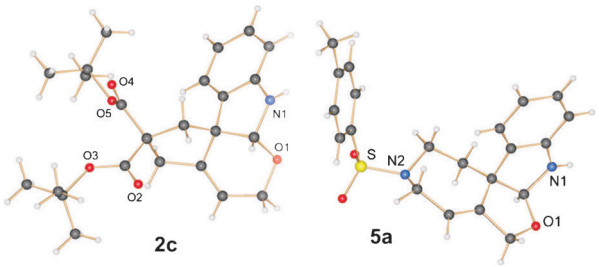
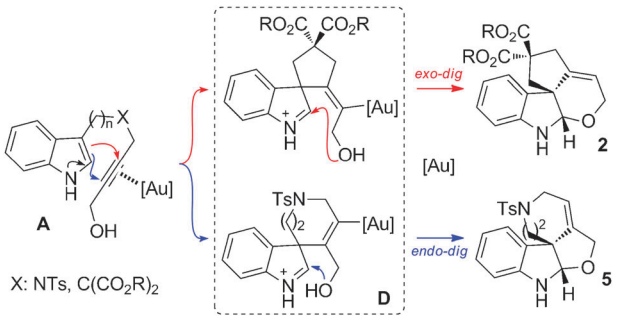


Fig. 3 Solid state structure of fused tetracyclic compounds **2c** (left) and **5a** (right).†



Scheme 1 Tentative mechanistic sketch.

In conclusion, we have documented an unprecedented atom/step economic synthesis of fused tetracyclic N(H)-free pyranyl indolines and furoindolines, *via* gold-catalyzed cascade cyclization. High levels of chemo-, regio- and diastereoselectivity were obtained for a range of densely functionalized compounds. Further studies into the development of an enantioselective variant of the protocol along with a detailed mechanistic investigation are currently underway in our laboratory.

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

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