ORGANIC LETTERS

2012
Vol. 14, No. 5
1350–1353

Enantioselective Gold-Catalyzed Synthesis of Polycyclic Indolines

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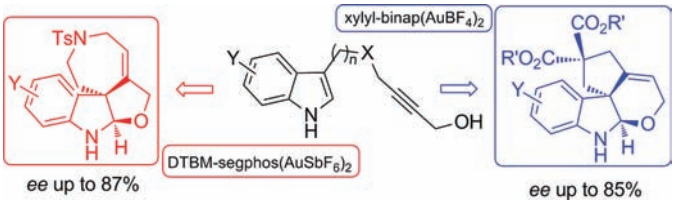
Received February 6, 2012

ABSTRACT



The synthesis of architecturally complex polycyclic fused indolines is achieved in a chemo-, regio-, and stereodefined manner, via an enantioselective gold-catalyzed cascade hydroindolination/iminium trapping synthetic sequence. Highly functionalized tetracyclic fused furoindolines (2) and dihydropyranylindolines (4) are synthesized in moderate to good yields and enantiomeric excesses of up to 87%.

Enantioselective gold catalysis continues to inspire and influence developments in organic synthesis,[1] providing reliable solutions to the current demand for selective and sustainable synthetic methodologies.[2] The stereoselective manipulation of unfunctionalized unsaturated hydrocarbons has greatly benefited from the rediscovery of asymmetric gold catalysis, with applications in the synthesis of complex molecular architectures.[3]

The proven pharmacological activity of indole alkaloids,[4] combined with their challenging molecular skeletons, concurs to define this class of polycyclic fused indolyl compounds as intriguing synthetic exercises for organic chemists.[5] In this segment, although catalytic asymmetric methodologies have already provided reliable solutions,[6] there is still an urgent need for sustainable and enantioselective protocols for their preparation.

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10.1021/ol300297t
Published on Web 02/15/2012

Our recent interests in the stereoselective manipulation of indolyl cores[7] drove our attention toward the exploitation of the well-established regioselective gold-catalyzed hydroindolination of alkynes[8] as a rapid and direct access to polycyclic fused indolines. Interestingly, despite the large amount of effort in this research line,[9] to the best of our knowledge no examples of enantioselective variants have been reported so far.[10]

In this communication we describe an unprecedented enantioselective gold-catalyzed cascade reaction of functionalized propargylic alcohols[11] leading to N(1)-unprotected indolines carrying additional 6/5-fused (**A**) and 5/7-fused (**B**) ring connections.

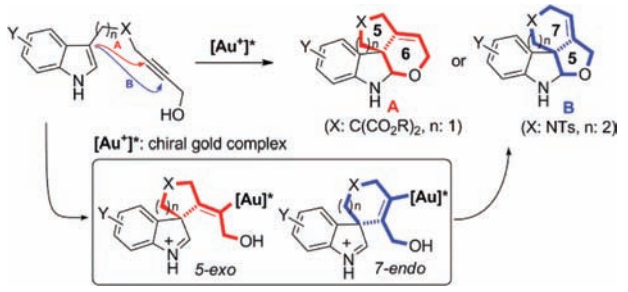


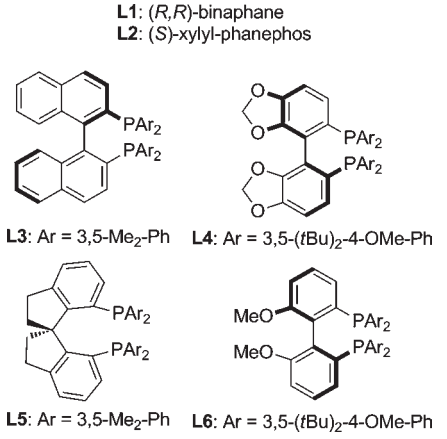
Figure 1. Working hypothesis: enantioselective synthesis of polycyclic indolines via gold-catalyzed cascade reactions (merely speculative stereochemical descriptors are reported).

Hydroarylation of the carbon−carbon triple bond and subsequent iminium trapping, operated by the alkenylgold intermediates,[12] constitute the hypothetical reaction machinery (Figure 1).[13]

At the outset of the present investigation we envisioned that, as the overall stereochemistry of the final product (**A** or **B**) is essentially ruled by the initial gold-triggered regioselective hydroindolination of the triple bond, the use of chiral gold complexes could theoretically open access to the unprecedented enantioselective gold-catalyzed synthesis of indolines carrying all-carbon quaternary stereocenters at the C(3) position.

Aiming to discover the optimal reaction parameters, we first underwent a screening of reaction conditions (namely, ligands, solvent, gold counterions, and temperature) by selecting **1a** as a readily available and synthetically flexible model acyclic precursor (Table 1).

Chart 1. Chiral Ligands Tested in the Optimization of the Catalytic System



A range of chiral C_2-symmetrical bis-phosphine ligands (**L1**−**6**, 5 mol %, Chart 1) were initially tested in the cascade reaction by preparing *in situ* the corresponding cationic binuclear gold complexes of the general formula $L(AuSbF_6)_2$ (entries 1−6, Table 1).[14]

Remarkably, in all cases 5-*exo*-*dig* regiochemistry was obtained exclusively, and among the ligands tested, (*R*)-xylyl-binap ligand **L3** provided **2a** in higher stereoinduction (*ee* = 56%) and moderate yield (65%, entry 3). The role of the gold counterion was then evaluated in the presence of **L3** (entries 7−11). Here, while the use of *para*-NO_2-benzoate (*p*NBn) did not promote the reaction at all, the addition of AgOTf and $AgBF_4$ provided **2a** in comparable yield (60%) and *ee* up to 74% (entry 9). Gratifyingly, by lowering the temperature at 0 °C and in the presence of 4 Å MS, (6a*R*,11b*R*)-**2a** was isolated in

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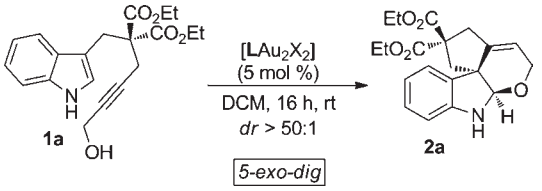
Table 1. Enantioselective Synthesis of the Dihydropyranylindoline **2a**[a]



entry	L	AgX	yield (%)[b]	*ee* (%)[c]
1	(*R*,*R*)-**L1**	$AgSbF_6$	21	46 (+)
2	(*S*)-**L2**	"	26	20 (−)
3	(*R*)-**L3**	"	65	56 (−)
4	(*S*)-**L4**	"	36	14 (−)
5	(*R*)-**L5**	"	61	0
6	(*S*)-**L6**	"	65	17 (−)
7	(*R*)-**L3**	AgOTf	59	72 (−)
8	(*R*)-**L3**	$AgNTf_2$	80	27 (−)
9	(*R*)-**L3**	$AgBF_4$	60	74 (−)
10	(*R*)-**L3**	$AgPF_6$	70	70 (−)
11	(*R*)-**L3**	Ag*p*NBn	traces	--
12[d]	(*R*)-**L3**	$AgBF_4$	89	86 (−)
13[e]	(*R*)-**L3**	$AgBF_4$	72	82 (−)
14[d,f]	(*R*)-**L3**$(AuCl)_2$	$AgBF_4$	82	84 (−)

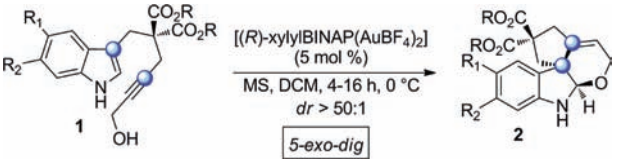
[a] All the reactions were carried out under a nitrogen atmosphere with anhydrous solvents. **2a** was always isolated as a single diastereoisomer. The precatalytic cationic dinuclear complexes were synthesized in situ, unless otherwise specified. [b] Isolated yields after flash chromatography. [c] Determined by HPLC analysis with chiral column. [d] Reaction at 0 °C, 4 h, in the presence of activated 4 Å MS. [e] In the presence of activated 5 Å MS. [f] Preformed gold complex was utilized. **L1**, (*R*,*R*)-binaphane; **L2**, (*S*)-xylyl-phanephos; **L3**, (*R*)-xylyl-binap; **L4**, (*S*)-DTBM-segphos; **L5**, (*R*)-xylyl-SDP; **L6**, (*S*)-MeO-biphep; *p*NBn, *para*-NO_2-benzoate.

89% yield with 86% *ee* (entry 12). Finally, the use of activated 5 Å MS (entry 13) or the preformed **L3**$(AuCl)_2$ (entry 14) complex did not lead to substantial variations (*ee* up to 84%) with respect to the optimal reaction parameters.

Encouraged by the results obtained in the standard cascade reaction assays, we verified the generality of the method by subjecting a series of N(H)-free indole propargylic alcohols **1b**−**i** to standard cyclization conditions, and the results are summarized in Table 2. In the presence of 5 mol % of (*R*)-[**L3**$(AuBF_4)_2$], satisfactory yields (50−75%) were obtained over a range of indole substitutions as well as malonyl tethering units. In all cases, corresponding tetracyclic indolines **2b**−**i** were isolated with excellent chemo- and diastereoselectivity (> 50:1). In particular, the nature of the "R" group did not impact the stereochemical profile of the reaction course, with a slight increase in enantioselection (*ee* = 87%), when bulky (tBu)$_2$-malonyl derivative **1b** was utilized (entry 1).

Moreover, both electron-withdrawing (i.e., halogen atoms) and electron-donating (i.e., MeO, Me) substituents were tolerated equally well in different positions (C(5) and C(6)) of the indole periphery. In particular, 5-OMe substituted alcohols **1f,i** reacted smoothly under optimal

Table 2. Scope of the Reaction[a]



entry	1	$R/R_1/R_2$	yield (%)[b]	*ee* (%)[c]
1	**1b**	tBu/H/H	65	87
2	**1c**	Me/H/H	60	76
3	**1d**	Et/Br/H	75	81
4	**1e**	Et/Cl/H	70	75
5	**1f**	Et/MeO/H	50	76
6	**1g**	Me/Cl/H	58	83
7	**1h**	Et/H/Cl	67	84
8	**1i**	tBu/MeO/H	51	77

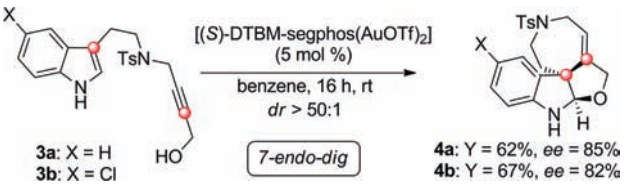
[a] All the reactions were carried out under a nitrogen atmosphere with anhydrous solvents. Compounds **2** were always isolated as a single diastereoisomer. [b] Isolated yields after flash chromatography. [c] Determined by HPLC analysis with a chiral column.

conditions providing the corresponding cyclized compounds **2f,i** with *ee* up to 77%. Analogously, 5- and 6-halo-derivatives (**2d**−**e**,**g**−**h**) led to the tetracyclic dihydropyranylindolines with enantiomeric excesses ranked between 75% and 84%.

Finally, the scope of the reaction was expanded further proving the competence of readily accessible alcohols **3** as acyclic precursors in the present gold-catalyzed process. In particular, tryptamine derivatives **3a,b** underwent cyclization via a preferential 7-*endo-dig* regiochemical pathway leading to tetracyclic furoindolines **4**, carrying a fused aza-substituted unsaturated seven-membered cycle. Interestingly, optimal results were recorded by subjecting model substrates **3a**,**b** to reaction conditions involving (*S*)-DTBM-segphos$(AuOTf)_2$ as the chiral catalyst (5 mol %) and benzene as the solvent (see Supporting Information for further details). In particular, diastereomerically pure furoindolines (7a*R*,12b*S*)-**4a,b** were isolated in satisfying yields and enantiomeric excesses up to 85% (Scheme 1).

Absolute configurations of the indolines **2b** and **4a** were unambiguously determined by simulation of their electronic circular dichroism spectra and $[\alpha]_D$ values by means of the TD-DFT approach.[15]

Scheme 1. Enantioselective Synthesis of Tetracyclic Furoindolines **4**, via 7-*endo-dig* Cyclization Pathway



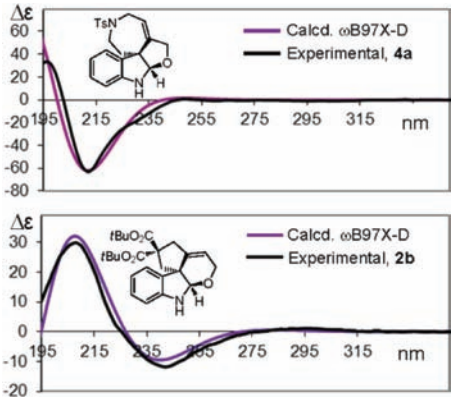


Figure 2. TD-DFT simulations of the electronic circular dichroism spectra of compounds **2b** and **4a**. The black traces correspond to the experimental spectra. The purple lines show the simulations obtained assuming the 7a*R*,12b*S* configuration for **4a** and the 6a*R*,11b*R* configuration for **2b**.

The ECD spectra calculated for the 7a*R*,12b*S* absolute configuration of **4a** and for the 6a*R*,11b*R* configuration for **2b** showed very good agreement with the experimental spectra of the major enantiomers (Figure 2). Also the calculated $[\alpha]_D$ values matched well with the experimental signs and values, thus enforcing the reliability of the assignment.

In conclusion, we have documented an unprecedented enantioselective cascade reaction for the preparation of tetracyclic fused indolines via gold-catalyzed hydroindolination of propargylic alcohols.

The ready availability of the acyclic precursors, the mild reaction conditions, and the good levels of regio-, diastereo-, and enantioselectivity nominate the protocol as a rapid entry to stereodefined polycyclic indoline alkaloids.

Acknowledgment. Acknowledgment is made to Progetto FIRB "Futuro in Ricerca" *Innovative sustainable synthetic methodologies for C−H activation processes* (MIUR, Rome) and University of Bologna (RFO funds).

Supporting Information Available. Experimental details, characterization data, NMR spectra, chiral HPLC chromatograms, optimization catalytic system, and details on the absolute configuration determination. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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