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Accessing chemical diversity by stereoselective gold-catalyzed manipulation of allylic and propargylic alcohols*

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Abstract: The combined use of asymmetric Au(I) catalysis with allylic as well as propargylic alcohols proved to be a competent synthetic tool, toward the realization of complex molecular organic architectures in a stereochemically defined manner. In particular, allylic alcohols have been utilized as alkylating agents in the synthesis of tetrahydrocarbazoles/carbolines and morpholines by means of new C–C and C–X bond-forming processes. Analogously, the direct activation of indole-propargylic alcohols with cationic Au complexes opened a direct access to tetracyclic fused indolines in a highly stereoselective manner.

Keywords: asymmetric catalysis; gold; heterocyclic chemistry.

INTRODUCTION

Organic as well as organometallic catalysis is receiving growing attention in the realm of enabling synthetic techniques, with always increasing applications in the pharmaceutical industry [1]. In particular, very recently, the organic synthetic scenario has been revolutionized by the boom in homogeneous Au catalysis [2]. The renaissance of this coinage metal allowed unprecedented transformations to be realized in a highly selective manner and rendered "old chemistry" more accessible from a practical point of view. Particularly, organic compounds containing unactivated C–C multiple bonds benefited from the high carbophilicity of Au species, which provided ready access to a great chemical diversity through direct and selective π-electrophilic activation.

Similarly, the replacements of hazardous chemical reagents with more environmentally acceptable analogous is a current hot synthetic challenge for modern organic chemistry. In this direction, the use of π-activated alcohols (namely: allylic, benzylic, and propargylic), as alkylating agents, is highly desirable owing to some peculiar features such as: (1) large availability at reasonable prices; (2) shortening of the synthetic sequence; and (3) greenness [3].

Among unfunctionalized unsaturated hydrocarbons, unactivated carbon–carbon double bonds are commonly reluctant in taking part to direct hydro-functionalization reactions. High temperatures, prolonged reaction times, and relatively high loading of catalyst are generally required. These stringent aspects are magnified if compared with analogous nucleophilic additions to more reactive allenes.

In this framework, despite the undoubted synthetic potential, the enantioselective Au-catalyzed electrophilic activation of "neutral" olefins is nearly unknown and only a limited number of examples

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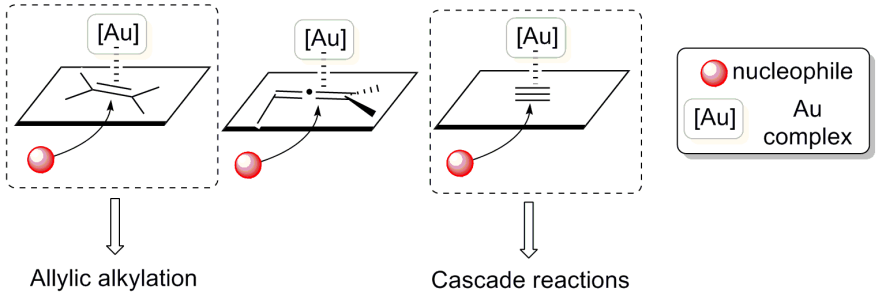


Scheme 1 Au-induced electrophilic activation modes of unsaturated hydrocarbons.

have been reported (Scheme 1) [4]. We envisioned the possibility to create new, sustainable, and direct routes to poly-functionalized heterocyclic motifs, by means of direct activation of π-activated alcohols as alkylating agents with chiral Au complexes [5].

Moreover, the efficiency of Au(I) catalysis in promoting new intramolecular cascade hydroindolination of propargylic alcohols is accounted, leading to tetracyclic fused indoline alkaloids in a highly stereoselective manner.

RESULTS AND DISCUSSION

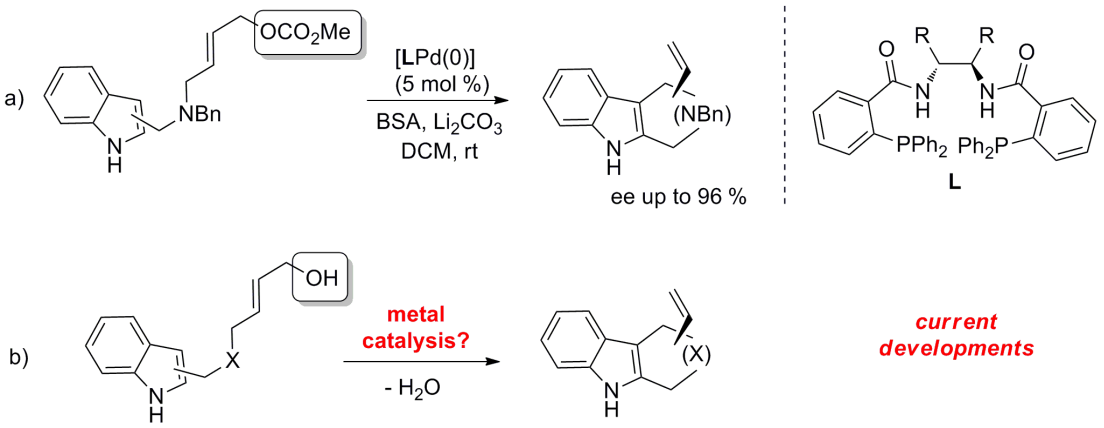
Allylic alcohols

Synthesis of tetrahydro-carbazoles/carbolines

Indole is a "privileged" molecular motif in complex naturally occurring compounds [6]. In this context, the chemical community is facing a growing demand for unprecedented sustainable catalytic and stereoselective methodologies for the functionalization of the indolyl core [7].

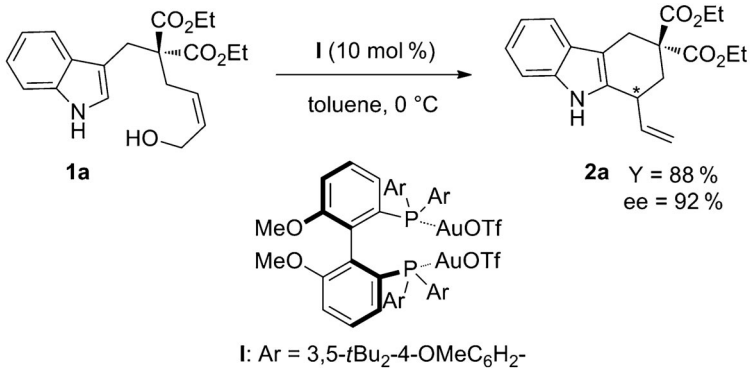
As a part of our ongoing interests in the catalytic "decoration" of this key heteroaromatic unit [6,8], we have previously documented the Pd-catalyzed enantioselective intramolecular allylic alkylation of indoles under Tsuji–Trost conditions for the synthesis of tetrahydro-β/γ-carbolines in a highly regio- and enantioselective manner [9]. A natural extension of the methodology would involve the employment of primary allylic alcohols instead of activated carbonates as alkylating agents. The new protocol would introduce several advantages in the final process, however, modest reactivity and poisoning phenomena exerted by the water released during the reaction course could make the search for optimal metal catalysts a challenging task (Scheme 2).

At the outset of the investigation, we identified in the synthesis of 1-vinyltetrahydrocarbazoles (**2**) a reliable benchmark process for the optimization of the reaction parameters. Interestingly, among the late transition metals investigated, only chiral cationic binuclear Au(I) complex **I** worked smoothly in promoting the desired intramolecular allylic alkylation.



Scheme 2 (a) Pd-catalyzed enantioselective synthesis of vinyltetrahydrocarbolines [9]. (b) Can alcohols be directly utilized in enantioselective allylic alkylations?

In particular, 1-vinyltetrahydrocarbazole **2a** was isolated in 88 % yield and 92 % enantiomeric excess when 10 mol % of DTBM-MeO-biphep(Au_2OTf_2) was employed in toluene at 0 °C (DTBM, 3,5-*t*Bu_2-4-$MeOC_6H_2$–, Scheme 3) [10]. Optimal reaction conditions were identified upon an extensive survey of variables including chiral ligands, solvents, temperatures, and metal counterions. The methodology proved to be general in terms of chemical diversity, with the possibility to synthesize both 1-vinyl and 4-vinyltetrahydrocarbazoles in good yields and high enantiomeric excesses. Moreover, by replacing the malonyl tethering unit with a nitrogen-containing group, 4-vinyltetrahydro-β-carbolines were also accessible with enantiomeric excesses up to 86 % [11].

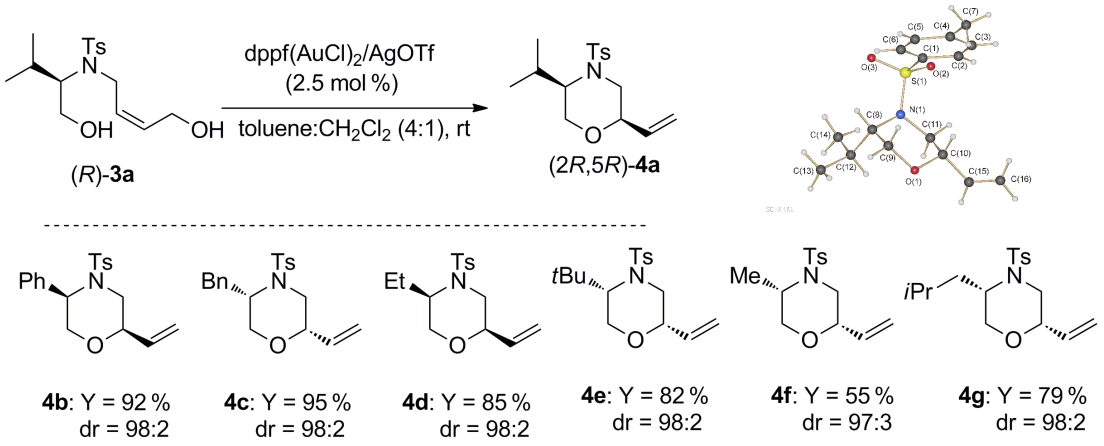


Scheme 3 Enantioselective Au-catalyzed allylic alkylation of indoles with alcohols.

Synthesis of 2-vinyl-morpholines

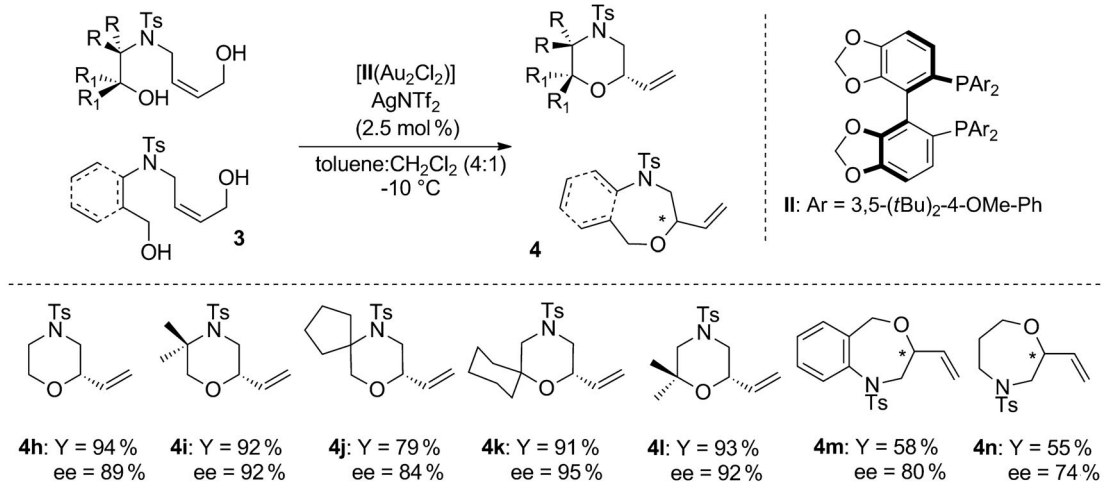
Morpholines are a class of synthetically relevant building blocks for natural product synthesis and auxiliaries in asymmetric synthesis [12]. Currently, several stepwise asymmetric methodologies have been developed for their preparation, however, catalytic and stereoselective synthetic approaches still remained elusive [13]. Prompted by the encouraging results previously documented on the direct use of allylic alcohols in intramolecular alkylations of indoles [14], we decided to verify the extendability of the Au-catalyzed process to the preparation of 2-vinyl-morpholines **4**, by means of dehydrating oxa-allylic alkylation in the presence of readily available diols (**3**). Firstly, we addressed our interest toward

the preparation of diastereomerically defined morpholine **4a**, starting from enantiomerically pure diol (*Z*)-**3a**. Interestingly, in this case dppf(AuNTf)$_2$ (2.5 mol %) proved to be the catalyst of choice, providing **4a** in a nearly quantitative manner and high diastereomeric ratio (25:1) in favor of the 1,4-*cis*-isomer [15]. The *cis* relative configuration of **4a** was established unequivocally by means of X-ray crystallography (Scheme 4). Simultaneously, the generality in the scope of the process was assessed by subjecting a range of enantiomerically pure diols to the best reaction conditions, and in all cases the desired substituted 2-vinyl-morpholines **4** were isolated in excellent yields and diastereoselectivity.



Scheme 4 Diastereoselective synthesis of substituted 2-vinyl-morpholines **4** via Au catalysis.

The enantioselective variant of the reaction was subsequently developed on the achiral model substrate (*Z*)-**3h**. Here, optimal outcomes were derived by the replacement of the dppf ligand with enantiomerically pure (*R*)-DTBM-segphos (**II**) and by adopting AgNTf$_2$ as the metathesis reagent. The NTs-2-vinyl-morpholine **4h** was isolated in 94 % yield and 89 % enantiomeric excess (Scheme 5).



Scheme 5 Asymmetric synthesis of six- and seven-membered heterocyclic compounds by means of enantioselective Au-catalyzed intramolecular allylic alkylation with alcohols.

Moreover, the synthesis of seven-membered 1,4-oxazepanyl rings was also realized. In these cases, a higher catalyst loading (5 mol %) was required to give the corresponding products **4m** and **4n** in 74 and 80 % ee, respectively.

Activation mode of the allylic alcohol frameworks to cationic binuclear Au catalysts

At the outset of our investigations, we considered the intrinsic "chelating" architecture of the allylic alcohol [i.e., soft π-base center (C=C bond) and hard σ-base unit (hydroxyl group)] as a potential guideline for the searching of a suitable metal catalyst [16]. In particular, the combination of cationic monometallic [Pt(II)]- or dinuclear cationic [Au(I)]-complexes [17] and allylic alcohols could result in a rigid bidentate coordination mode that is a desirable prerequisite for achieving high levels of stereoinduction in asymmetric metal catalysis (Fig. 1) [18].

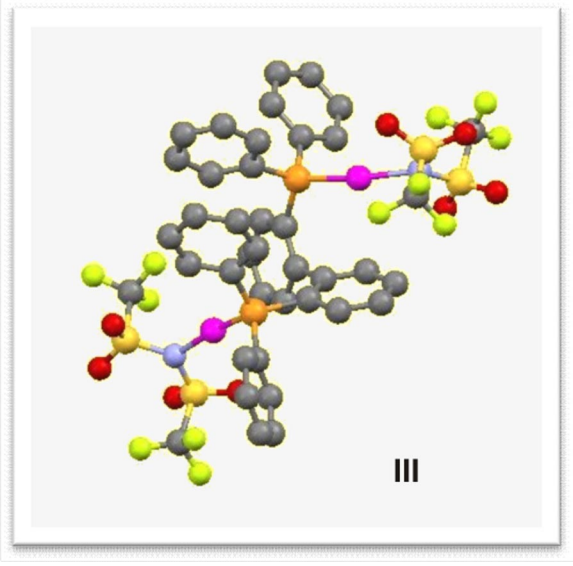
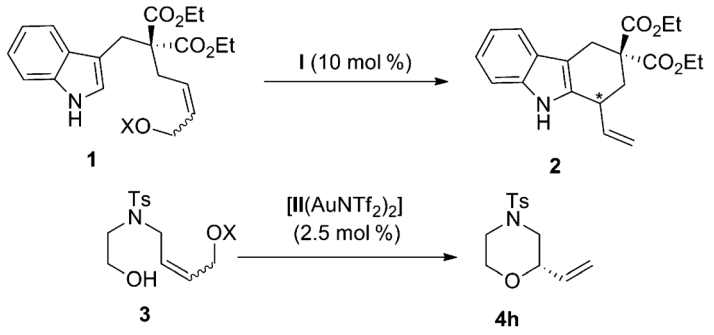


Fig. 1 Crystal structure of the $[Au_2(biphep)(NTf_2)_2]$ complex **III**.

Experimentally, the key role played by the –OH group on the final output of the process was demonstrated for both syntheses of polycyclic indoles and morpholines. As a matter of fact, when optimal reaction conditions were applied to the O-protected precursors (OMe, or OTBDMS) interesting results were obtained (Table 1). In particular, significant drops in both chemical and enantioselectivity were recorded in the presence of small (Me) and sterically demanding (TBDMS) O-capping substituents. This evidence calls for an active role of the leaving hydroxyl-group in providing the active species, perhaps exerting intramolecular hydrogen-bonding contacts (folding effects) [19] or favoring more rigid aggregates between substrate and cationic dinuclear Au complex (vide infra). Further corroboration to this conclusion resulted from the chemical outcomes recorded with acyclic precursors featuring C–C double bonds with *Z* or *E* configurations (Table 1, entries 5–8). Different orientation of the OH group in the space impacted significantly into the ring-closing procedure [20], highlighting that only *Z*-olefins proved to be competent substrates in our methodologies. Interestingly, while in the carbazole synthesis the use of (*E*)-**1a** proved to be completely inert (entry 6), the corresponding (*E*)-**3h** provides the morpholine **4h** with complete inversion of stereoinduction (entry 8). At this stage, it should also be noted that the expected π-(C=C)–Au interaction with *E*- or *Z*-isomers would result in a couple of diastereomeric Au(I)-π complexes with **1a** or **3h**.

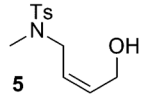
Table 1 Proving the role of the leaving hydroxyl-group and configuration of the C=C bond in the Au-catalyzed enantioselective synthesis of tetrahydrocarbazoles and morpholines.



Entry	Precursor	Config. C=C	Yield (%)	Ee (%)
1	**1b** (X = Me)	Z	Traces[a]	–
2	**1c** (X = TBDMS)	*Z*	48	56
3	**3p** (X = Me)	*Z*	19	8
4	**3q** (X = TBDMS)	*Z*	Traces	–
5	**1a**	Z	88	92
6	**1a**	*E*	nr[b]	–
7	**3h**	Z	94	89
8	**3h**	*E*	59	–66

[a]The unreacted **1c** was recoved with *E*-configured C=C double bond. Such evidence is reationalizable in terms of auration/rotation/deauration sequence of the C=C.
[b]nr = no reaction.

With the purpose of gaining further insight into these intriguing findings, we synthesized the model complex $[Au_2(biphep)(NTf_2)_2]$ **III** (83 % yield) and obtained the corresponding X-ray structure by slow evaporation from diluted solution of CD_2Cl_2. From the structure reported in Fig. 1, it is evident that the usual linear coordination geometry of the two Au(I) atoms when coordinated by one P atom of the bridging biphep scaffold [P-Au-N 172.4 and 174.3(1)º]. In addition, the long Au···Au distance of 6.6818(6) ruled out any kind of aurophilic interaction in the solid state, which is probably ascribable to the higher steric hindrance of NTf_2^- anion than the chloride [21]. The complex **III** was then utilized in combination with compound **5** in a variable-temperature NMR spectroscopic investigation, in order to mimic the active cat/substrate coordination geometry in the stereoselective ring-closing process.

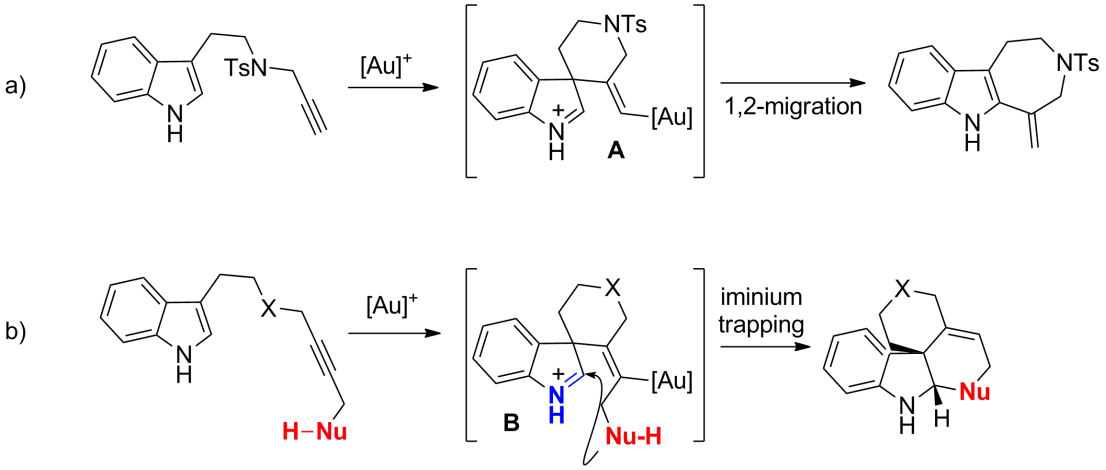


Here, $^{31}P/^{13}C$ NMR analysis revealed the expected coordination of the preformed cationic di-Au complex **III** with **5** (Au···C=C), however, the unambiguous definition of weak contacts between the leaving hydroxyl group of **5** and complex **III** turned out to be unrealizable. For the case of the morpholine synthesis, the key role of the Au counterion was also extensively investigated, providing a range of scattering results (i.e., **4a**, OTf^-: yield = 69 %, ee = 68 %; SbF_6^-: yield = 58 %, ee = 50 %; BF_4^-: yield = 80 %, ee = 23 %, OTs^-: yield = 22 %, ee = –26 %). The latter findings clearly emphasized the involvement of the counterion in the enantiodiscriminating step of the reaction.

As summary, although a conclusive response is still lacking, we can envision two possible scenarios accounting for the coordination mode of the acyclic precursors **1** and **3** to cationic P-P(AuX)$_2$ complexes. In particular, it appeared clear that, beside the preventable Au···C=C coordination, weak hydrogen bond interactions are pivotal in delivering rigid conformations through the presumable assistance of the counterion. As a consequence, we can speculate that the second Au atom could act either as a mere spectator, perhaps stabilizing the Au intermediates through aurophilic interactions [22] or, alternatively, being involved in a bridged arrangement through the OH···X network, capable of bringing steric as well as electronic diversity in proximity of the reaction site. In the first hypothesis, the counterion X should act as a folding agent, by bridging the leaving OH and the acid hydrogen atom of the nucleophilic unit [i.e., *N*(1)H for indoles and OH for morpholines].

Propargylic alcohols

Electrophilic activation of internal as well as terminal alkynes by Au(I) species is by far the most popular application of Au catalysis in organic synthesis [23]. The unique alkynophilicity exerted by Au(I) complexes/salts allowed unprecedented and selective transformations of C–C triple bonds under mild conditions. Moreover, the relative stability of Au-alkylidene intermediates was extensively exploited for the construction of functionalized polycyclic fused molecular architectures by means of cascade reactions [24]. In this field, the Au-catalyzed hydroindolination of unfunctionalized alkynes was recently documented by Echavarren and co-workers in a chemoselective manner [25]. The processes generally ended up with the re-aromatization event of the indole nucleus through a 1,2-migration (Scheme 6a). The isolation of spiro-indolyl derivatives accounts for the initial attack of the highly nucleophilic C3 position leading to Au-alkylidene intermediates (**A**).



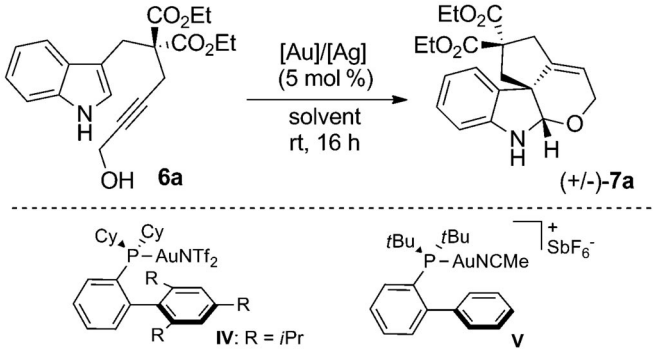
Scheme 6 (a) Au-catalyzed intramolecular hydroindolination of unfunctionalized alkynes [23]. (b) Working plan for the synthesis of polycyclic fused indolines via Au-catalyzed cascade cyclization.

We envisioned the possibility to channel the reaction course toward complex tetracyclic fused indolines simply by intercepting the electrophilic iminium species (**B**) with a nucleophilic group that could be previously installed in the internal acetylene unit (Scheme 6b) [26].

The readily available indole propargylic alcohol **6a** was elected as a model substrate to verify the working plan, and subjected to the ring-closing reaction in the presence of a range of Au(I) or Au(III) salts/complexes. From the collection of results listed in Table 2, several conclusions can be drawn:

- a 5-*exo-dig* pathway was exclusively observed in all the reaction conditions examined;
- cationic Au(I) species displayed greater propensity to catalyze the cascade reaction with respect to Au(III) analogous (entries 1,2 vs. 3–8);
- the desired dihydropyranylindoline **7a** was obtained as a single diastereoisomer; and
- among the catalysts scrutinized, the well-defined silver-free complex **V** [27] emerged as the catalyst of election, providing **7a** in 74 % yield (entry 6) [28].

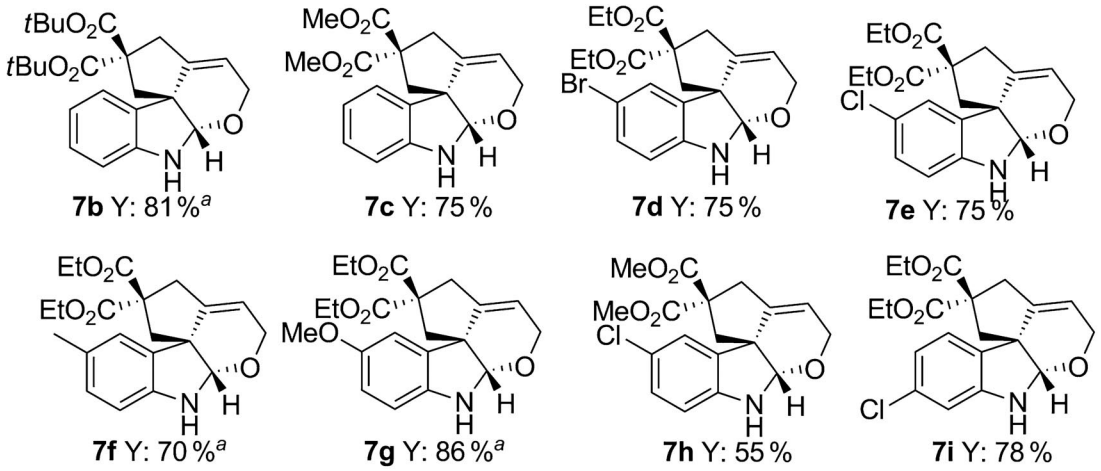
Table 2 Screening of Au catalysts for the diastereoselective synthesis of tetracyclic fused indoline **7a**.



Entry	[Au]/[Ag]	Solvent	Yield (%)
1	$AuCl_3$	Toluene	10
2	$AuCl_3$/AgOTf	Toluene	33
3	PPh_3AuOTf	DCM	45
4	[AuIMes]OTf	DCM	55
5	**IV**	DCM	60
6	**V**	DCM	74
7	**V**	MeOH	61
8	**V**	$MeNO_2$	63

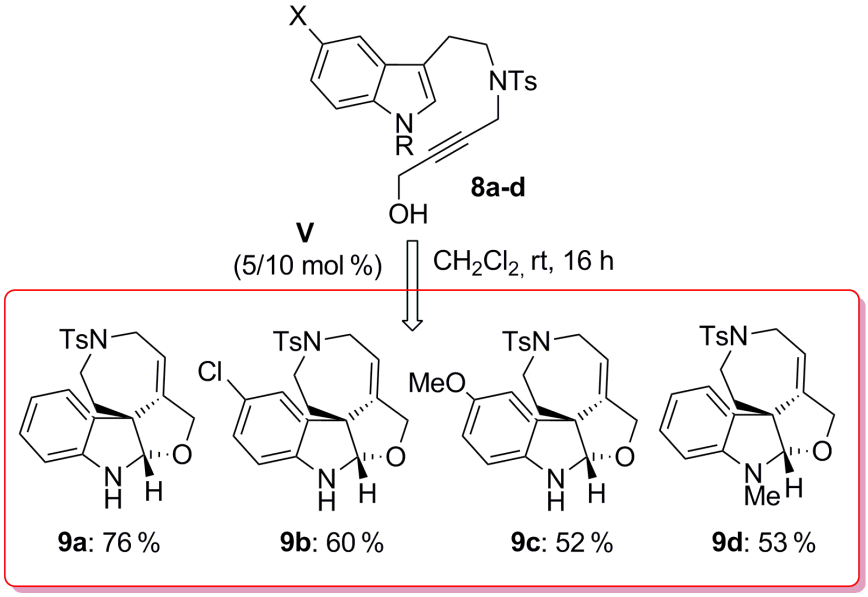
Scope and limitations of the method, with regard to the substrate, were subsequently examined by subjecting a small library of propargylic alcohols **6b–i**, featuring malonyl units as tethering frameworks, to the cascade cyclization (**V**: 5 mol %, DCM, rt, 16 h). Moderate to good isolated yields (55–86 %) and excellent diastereoselectivity were always combined with the persistence of a 5-*exo-dig* regiochemistry [29].

The data collected in Scheme 7 clearly highlight the tolerance of the protocol toward the decoration of the indolyl core with both EDGs (**7f,g**) and EWGs (**7d,e,h,i**) in different positions. Moreover, the alkyl chain of the malonyl unit did not significantly affect the performances of the catalytic system.



Scheme 7 Substrate scope. [a]In the presence of 10 mol % of **V**.

Subsequently, the synthetic potential of the present Au-catalyzed cascade reactions was expanded further, by highlighting its compatibility to tryptamine derivatives **8a–d**. Interestingly, alcohols **8** led to the desired tetracyclic poly-functionalized furoindolines **9a–d** through an inverted regiochemical pathway (*7-endo-dig*) [30] and with moderate to good isolated yields (52–76 %, Scheme 8). Also, in this case only one diastereoisomer was detected in the reaction crude.



Scheme 8 Synthesis of the tetracyclic furoindolines from *N*Ts tryptamine precursors **8a–d**.

Finally, the molecular structures of **7**- and **9**-type polycyclized compounds were unambiguously elucidated via X-ray analysis of compounds **7b** and **9a** as reported in Fig. 2.

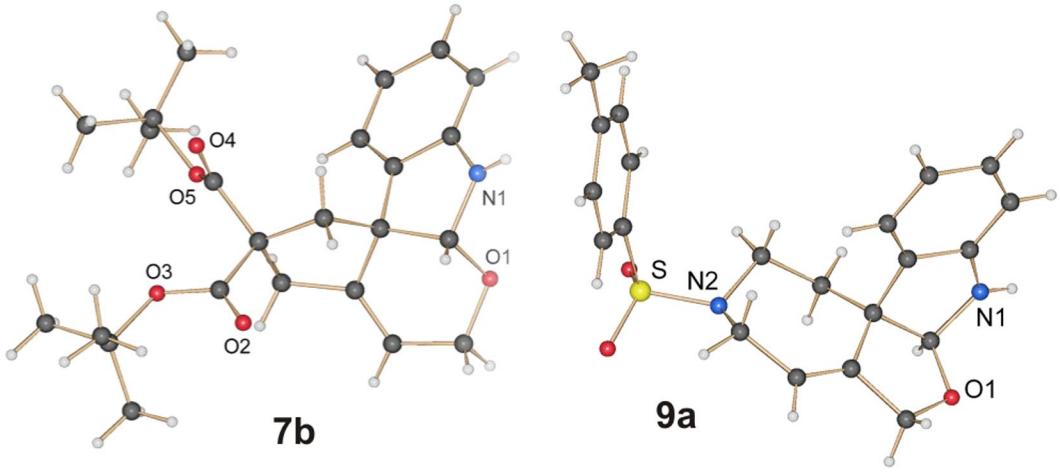


Fig. 2 Solid-state structure of fused tetracyclic indolines **7b** (left) and **9a** (right).

CONCLUSIONS

In spite of the remarkable achievements in asymmetric catalysis, there is still room for improvements both in the direction of the development of new transformations and toward the replacement of hazardous chemicals and waste production minimization in known protocols. The use of chiral Au complexes proved high efficiency in the direct electrophilic activation of allylic and propargylic alcohols toward the realization of unprecedented intramolecular cyclizations for the preparation of heterocyclic scaffolds. In particular, allylic alcohols demonstrated competence as sustainable alternatives to more reactive carbonates/acetates in enantioselective nucleophilic alkylation reactions, and indole propargylic alcohols generate a new class of tetracyclic indolines through a cascade catalytic event. Finally, chemo-, regio-, and stereoselection were efficiently addressed by the use of chiral cationic dinuclear Au species under mild reaction conditions, with complete atom economy or producing water as the only stoichiometric byproduct.

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