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Allylic alcohols: Valuable synthetic equivalents of non-activated alkenes in gold-catalyzed enantioselective alkylation of indoles

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ABSTRACT

The recent booming of gold catalysis has demonstrated that unprecedented transformations can be realized in a highly selective manner. Moreover, due to the growing availability of chiral organic ligands, gold-catalysis can be considered as one of most dynamic hot spots in asymmetric synthesis. However, in this context, the use of non-activated olefinic C–C double bonds is still largely unexplored due to the intrinsic inertness of C=C (respect to allenes and alkynes) in taking part in nucleophilic additions assisted by π-electrophilic activations. Allylic alcohols have been demonstrated to be feasible "surrogates" of non-activated alkenes for the enantioselective allylic alkylation of indoles catalyzed by chiral gold(I) complexes. In this investigation, a full account addressing efficiency and substrate scope of such a process is presented.

1. Introduction

The use of gold(I)-catalysis in organic transformations has unquestionably entered its *golden age* upon the exponential growth observed over the last decade [1]. This widespread interest is primarily ascribable to a number of unique properties featured by [Au(I)] species, such as: functional group/moisture tolerance, mildness of operating conditions, isohypticity (i.e. stability towards oxido-reductive processes) and dual-function acidity (σ and π). Furthermore, the large availability of chiral organic ligands concurs to define Au(I)-catalysis as one of the most dynamic hot spots in asymmetric synthesis [2].

The well-recognized carbophilicity of "*soft*" gold species has been widely utilized in electrophilic activation of π-electron-containing compounds (*e.g.* alkenes, alkynes, allenes) toward nucleophilic attack. Worth mentioning, the high level of chemo- and regioselectivity of these processes is rapidly revolutionizing the synthetic portfolio for the functionalization of activated as well as non-activated π-systems, by focusing on critical issues such as: mildness of experimental conditions, broadness of scope, atom economy and tolerance of functional groups.

However, differently by alkynyl and allenic frameworks, the stereoselective gold-catalyzed manipulation of non-activated olefins is still largely unexplored, due to their intrinsic inertness in taking part to nucleophilic additions [2b]. In fact, although several reports have efficiently addressed the gold-catalyzed activation of alkynes or allenes toward nucleophiles, the enantioselective gold-assisted electrophilic activation of olefins has been relatively poorly documented. In this context, worth mentioning is the elegant report by Widenhoefer and coworkers on the intermolecular hydroamination of 1-alkenes with ureas in the presence of chiral gold(I) complexes [3].

Related to this topic, we recently discovered that configurationally defined allylic alcohols can be used as effective synthetic equivalents of non-activated alkenes in stereoselective intramolecular allylic alkylation of indoles [4]. The reaction documented for the first time the direct gold(I)-catalyzed activation of alcohols in Friedel–Crafts-type alkylation (FCA) reactions and it represents a reliable alternative to the stereoselective Tsuji–Trost-type allylic alkylation of arenes [5]. It is noteworthy that, in terms of substrate availability and sustainability the direct employment of allylic alcohols is convenient because water is the only by-product of the alkylating event. Instead, the Pd/Ir/Mo-assisted methodologies require pre-installed [6] or *in situ* formed [7] leaving groups at the allylic positions in the prochiral electrophilic substrates, that are generally prepared from allylic alcohols.

In this context, we envisioned that the aptitude of gold(I) species to be involved in C=C electrophilic activation and the concomitant

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chelating coordination mode of chiral dinuclear gold complexes with the allylic alcohols could satisfy the mandatory requirements to obtain high levels of chemo- and stereoselectivity [8].

As a part of our ongoing research on the design and development of new catalytic and stereoselective methodologies for the *decoration* of arenes [9,10], we present here a full account on the use of chiral gold(I) π-Lewis acids for the enantioselective synthesis of vinyl-tetrahydro-β-carbazoles and tetrahydro-β-carbolines by means of direct alkylation of indoles with allylic alcohols [11].

2. Result and discussion

2.1. Working plan

Functionalized tetrahydrocarbazoles (THCs) [12] **A** and tetrahydro-β-carbolines (THBCs) [13] **B** are key molecular motifs frequently encountered in natural occurring polycyclic fused indolyl-based alkaloids (Fig. 1) [14]. Nowadays, a variety of synthetic methodologies for their preparation is available, [15] however, the stringent request for more ***s***imple, ***s***elective and ***s***ustainable synthetic routes justifies the ongoing interest of the scientific community in the field.

Our working plan to these classes of compounds relies on the gold-catalyzed intramolecular FC-type alkylation of the indolyl nucleus with allylic alcohols, that results in the introduction of a synthetically flexible vinyl group at the benzylic position (α or δ). Moreover, the transfer of chirality from enantiomerically pure dinuclear gold(I) complexes of general formula $[(PP)^*(Au_2X_2)]$ ($(PP)^*$: chiral C_2-symmetric biphosphine ligand) to the final polycyclic compounds would give access to stereochemically defined molecular architectures.

2.2. Synthesis of the acyclic precursors

At the outset of our investigation, we reasoned that the synthesis of configurationally pure allylic alcohol precursors was essential to pursue the final aim due to the prochiral nature of the C=C bond framework. To this aim, we excluded the use of poorly stereoselective C=C bond synthetic methodologies such as Wittig-type condensations or cross-metathesis reactions and we opted to install the pre-formed olefin moieties to properly functionalized indolyl cores. In particular, we identified in the readily available indolyl malonates **1**, **2** and indolyl methansulfonamides **3a**,**4a** as valuable building blocks for the FC-precursors (Scheme 1). Here, while the malonates **1**,**2** were synthetized as previously described

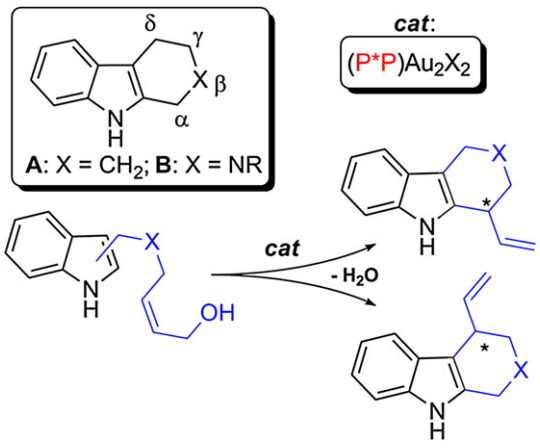
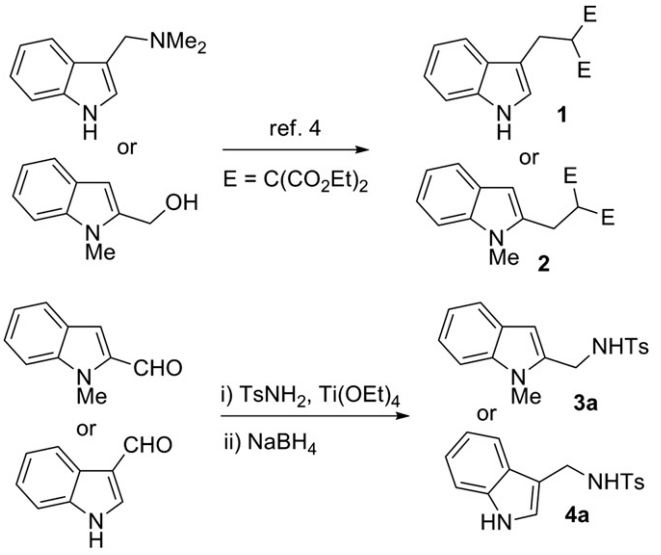


Fig. 1. Target compounds (**A**,**B**) and working plan.



Scheme 1. Synthesis of indolyl malonates **1**,**2** and indolyl methansulfonamides **3a**,**4a**.

[16], the methansulfonamides were obtained by the coupling of the indolyl 2- or 3-carboxaldehydes and $TsNH_2$ ($Ti(OEt)_4$, toluene, reflux) [17] followed by reduction with $NaBH_4$ (THF, 0 °C → rt).

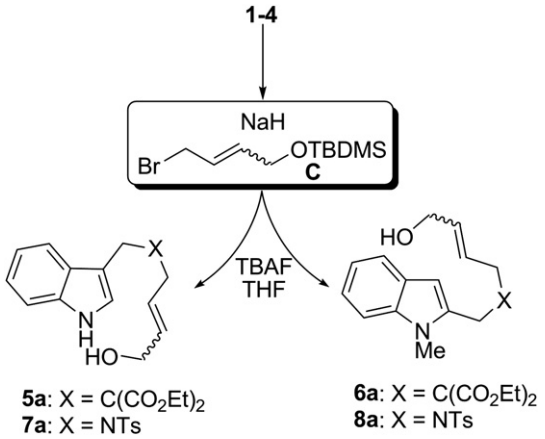
The indolyl derivatives **1**–**4** were then coupled with (*Z*)- or (*E*)-allylic bromides **C** under basic conditions (NaH, THF, reflux), then conventional removal of the protecting group (TBAF, THF, 0 °C → rt) afforded the corresponding indolyl-substituted allylic alcohols **5**–**8** in moderate yields (Scheme 2).

2.3. Gold-catalyzed ring-closure

In order to evaluate the applicability of asymmetric gold catalysis to the planned cyclization, we selected compounds **5a** and **8a** (Scheme 2) as model substrates, on which a survey of reaction conditions (ligand, gold-source, counterion) was undertaken.

First, a range of chiral C_2 symmetric phosphine ligands (**L1**–**L10**, Chart 1) were considered in promoting the ring-closure of **5a** in the presence of dinuclear gold complexes made from [AuCl (SMe_2)] and representative results are collected in Table 1.

As emerging from Table 1, good to high isolated yields were obtained (66–96%, excepted for DIOP **L5**, entry 5) working in toluene as the solvent at room temperature. However, it turned



Scheme 2. Synthesis of C-2/3 tethered indolyl-allylic alcohols **5a**–**8a** with allyl bromides **C**.

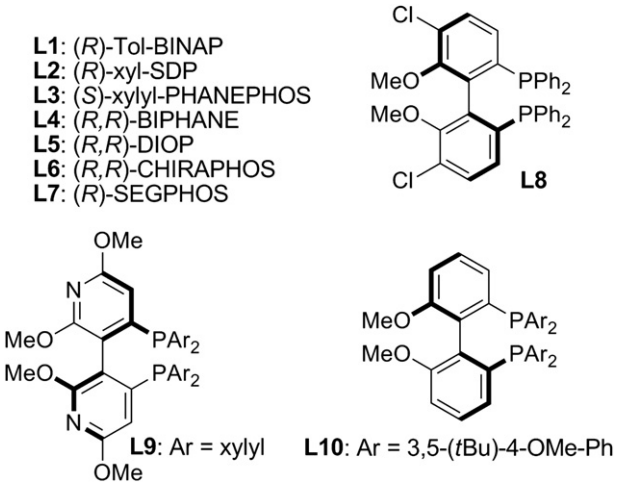


Chart 1.

out that (*S*)-3,5-*t*Bu-4-MeO-MeOBIPHEP **L10** proved to be the best ligand, leading to 1-vinyl-THC **9a** in 78% yield and ee = 88% (entry 10). Then, the role of the counterion was proved to be crucial for both reaction rate and stereoinduction, with OTf^- (trifluoromethanesulfonate) acting as the best counterion (entries 10–14). Moreover, by lowering the reaction temperature to 0 °C the enantiomeric excess increased up to 90%, meanwhile a high yield (95%) was obtained after 48 h (entry 15). Finally, it should be observed that pre-formed [18] or *in situ* assembled **L10**-(Au_2Cl_2) complex furnished comparable chemical outcomes (entry 15 *vs* entry 16) and when insoluble AgCl was removed by filtration from the reaction mixture no significant variations with respect to the best results were recorded (**9a**: yield = 69%, ee = 87%).

Table 1
Optimization of the reaction conditions for the intramolecular asymmetric allylic alkylation of (*Z*)-**5a**.

Entry[a]	L	AgX	Yield (%)[b]	ee (%)[c]
1	**L1**	AgOTf	72	−30
2	**L2**	AgOTf	85	9
3	**L3**	AgOTf	90	28
4	**L4**	AgOTf	95	29
5	**L5**	AgOTf	8	0
6	**L6**	AgOTf	95	0
7	**L7**	AgOTf	95	72
8	**L8**	AgOTf	77	35
9	**L9**	AgOTf	73	48
10	(*R*)-**L10**	AgOTf	78	88
11	(*R*)-**L10**	$AgBF_4$	55	87
12	(*R*)-**L10**	$AgSbF_6$	25	62
13	(*R*)-**L10**	AgOTs	10	92
14	(*R*)-**L10**	$AgNTf_2$	95	65
15[d]	(*R*)-**L10**	AgOTf	95	90
16[d,e]	(*S*)-**L10**	AgOTf	84	−90

[a] All the reactions were carried out in anhydrous toluene, under nitrogen atmosphere, pre-forming the catalyst in CH_2Cl_2. **L**/[Au]/[Ag]: 10/20/20 mol%, unless otherwise specified.
[b] Isolated yield after flash chromatographic purification.
[c] Determined by HPLC analysis with chiral column.
[d] At 0 °C, 48 h reaction time.
[e] Isolated **L10**-(Au_2Cl_2) complex was employed.

2.4. Scope and limitations of the catalytic protocol

The previously described outcomes of the FC-type reactions demonstrated that the best catalytic system (**L10**$(AuOTf)_2$, rt, 0 °C, toluene) proved generality for the synthesis of 1-vinyl- and 4-vinyltetrahydrocarbazoles in good extent. In particular, tolerance toward a wide range of functional groups (EWG and EDG) on the indole moiety was demonstrated and the desired 1-vinyl-THCs **9b–i** were isolated in 52–91% yield and ee of 80–96% (Fig. 2). Worth mentioning, the presence of a methyl group at the indole nitrogen prevented the ring-closing Friedel–Crafts alkylation, probably due to the detrimental sterical hindrance induced by the methyl group nearby the cyclization site (C2-position). The alkyl substituents of the ester functions (i.e. Me, *t*Bu, **5h,i**) did not significantly affect the chemical and stereochemical outcome, providing THCs with ee of 85% and 92%, respectively.

The methodology was then efficiently utilized for the FC-type alkylation of indolyl-alcohols **6a–e** bearing the unsaturated side-chain at the indole-C2 position. From the data depicted in Table 2 it turns out that the level of stereodifferentiation recorded in the formation of compounds **10a–e** (ee = 74–86%) was still synthetically interesting, although slightly lower than that of 1-vinyl-THCs **9**.

Although the synthesis of 4-vinyltetrahydro-β-carbolines **12** have been already addressed in our previous research projects, up to now, catalytic enantioselective methodologies have relied only on enantioselective Pd-catalyzed Tsuji–Trost allylic alkylation with carbonates [6a] or gold-catalyzed diastereoselective cyclizations (Scheme 3a and b) [19].

The results listed in Tables 2 and 3 prompted us to verify the extension of the protocol to the preparation of analogous polycyclic indolyl compounds bearing nitrogen atoms as tethering frameworks. To this aim model substrate (*Z*)-**8a** was obtained in straightforward manner through the synthetic route depicted in Scheme 2. Interestingly, treating **8a** under optimal reaction parameters, (*S*)-3,5-*t*Bu-4-MeO-MeOBIPHEP **L10** and (*S*)-xylyl-phanephos **L3** provided **12a** to a synthetically useful extent (yield = 71%/ee = 80% with **L3** and yield = 75%/ee = 80% with **L10**). On the contrary, other C_2-symmetric phosphine ligands (i.e. **L1** and **L2**) proved to be less efficient (entries 1,2, Table 3).

The scope of the reaction was then investigated with a range of (*Z*)-alcohols **8b–e**. Tolerance toward molecular functionalities on the indolyl ring was demonstrated with enantiomeric excesses ranking between 70% and 80%. Moreover, easily removable *N*(1)-allyl group [20] was also introduced into the alcoholic precursor (**8f**) and the corresponding THBC **12f** was obtained in comparable ee (78%, entry 10).

Interestingly, the configuration of the C–C double bond of the acyclic precursor played a key role both on the malonate and nitrogen-tethered substrates. As a matter of fact, allylic alcohols (*E*)-**5a** and (*E*)-**8a** were completely inert toward the cyclization conditions, probably due to an unfavorable spatial arrangement of the sterically demanding bimetallic catalyst. Such an evidence invokes a substrate-controlled mechanism, which is analogous to the gold-catalyzed hydroindolination of allenes [21].

Unfortunately, the methodology did not provide any encouraging result when applied to the synthesis of 1-vinyl-tetrahydro-γ-carbolines (THGCs). In fact, despite the numerous attempts, the cyclization of C3-substituted indolyl alcohol (*Z*)-**7a** failed in providing the desired THGC. The partial recovering of the starting material with the concomitant formation of substantial amount of unknown polymeric material was recorded (Scheme 4).

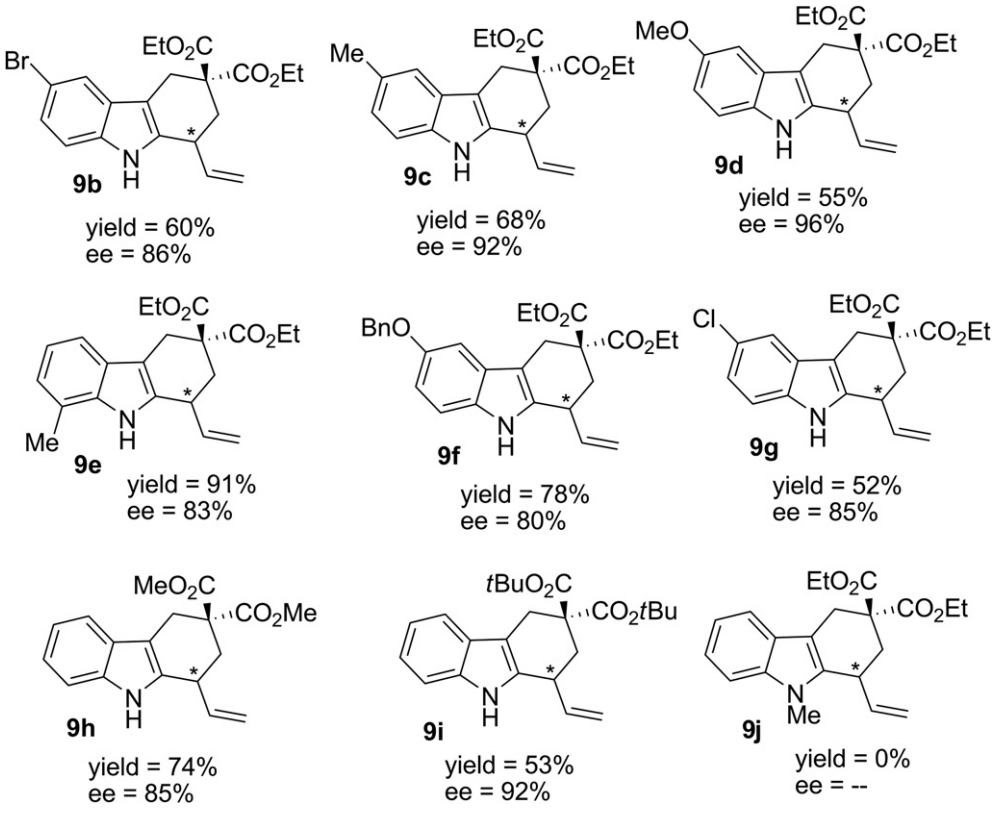


Fig. 2. Collection of 1-vinyl-THCs prepared by means of gold(I)-catalyzed allylic alkylation.

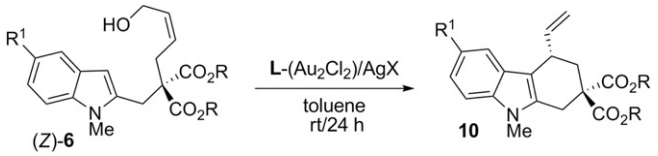
2.5. Determination of the absolute configuration

The absolute configuration of tetrahydrocarbazole **10b** and tetrahydro-β-carboline **12b** were unambiguously determined via chemical correlation and X-ray crystallography, respectively.

In particular, the vinyl group of the compound **10b** (ee = 80%) was reduced under heterogeneously Pd-catalyzed hydrogenation reaction to the corresponding δ-ethyl-THC **10f** (yield = 85%, ee = 74%), and the optical rotation value compared with that of the known compound [22]. In such a way, the absolute configuration of **10b** was determined to be *S*, and the configurations of **10a**,**c**–**e** assigned by analogy (Scheme 5).

Analogously, absolute configuration of THBCs **12b** was determined to be *S* by subjecting the THBC to single crystal crystallographic analysis (Fig. 3). Configurations of compounds **12a**,**c**–**f** were assigned by analogy.

Table 2
Catalytic enantioselective intramolecular FCA reactions. Synthesis of 4-vinyl-tetrahydrocarbazoles **10**.

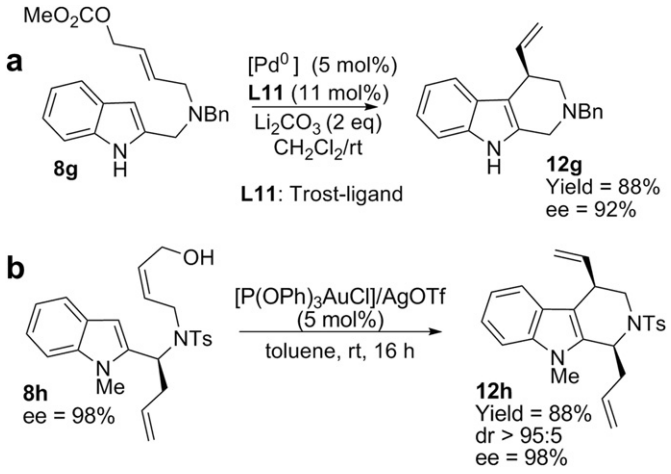


Entry[a]	Alcohol	R/R[1]	Product	Yield (%)[b]	ee (%)[c]
1	**6a**	Et/H	**10a**	79	86
2[d]	**6b**	*t*Bu/H	**10b**	80	80
3	**6c**	Me/H	**10c**	87	74
4	**6d**	Et/OMe	**10d**	55	83
5	**6e**	Et/Me	**10e**	87	80

[a] All the reactions were carried out in anhydrous toluene under nitrogen atmosphere, pre-forming the catalyst in CH_2Cl_2 (**L10**/[Au]/[Ag]: 10/20/20 mol%).
[b] Isolated yield after flash chromatographic purification.
[c] Determined by HPLC analysis with chiral column.
[d] Room temperature.

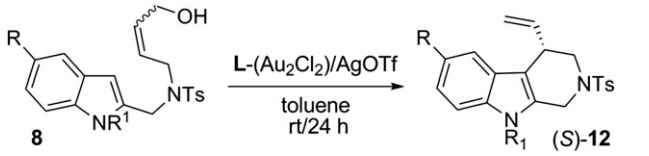
2.6. Mechanistic discussion

Due to the intrinsic "chelating" architecture of the allylic alcohol, featuring a *soft* π-base center (C–C double bond) and



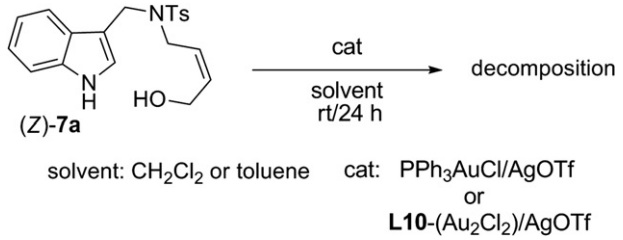
Scheme 3. (a) Enantioselective Pd-catalyzed allylic alkylation of indoles. (b) Diastereoselective gold-catalyzed synthesis of THBCs.

Table 3
Intramolecular asymmetric allylic alkylation of **8a-f**.



Entry[a]	L	Reagent	R/R[1]	Product	Yield (%)[b]	ee (%)[c]
1	**L1**	(*Z*)-**8a**	H/Me	**12a**	72	40 (*R*)
2	**L2**	(*Z*)-**8a**	H/Me	**12a**	50	56
3	**L3**	(*Z*)-**8a**	H/Me	**12a**	71	80
4	(*S*)-**L10**	(*Z*)-**8a**	H/Me	**12a**	75	80
5[d]	(*S*)-**L10**	(*Z*)-**8a**	H/Me	**12a**	62	68
6	(*S*)-**L10**	(*Z*)-**8b**	Cl/Me	**12b**	93	79
7	(*S*)-**L10**	(*Z*)-**8c**	Me/Me	**12c**	75	80
8	(*S*)-**L10**	(*Z*)-**8d**	OMe/Me	**12d**	61	76
9	(*S*)-**L10**	(*Z*)-**8e**	H/Bn	**12e**	95	70
10	(*S*)-**L10**	(*Z*)-**8f**	H/allyl	**12f**	72	78

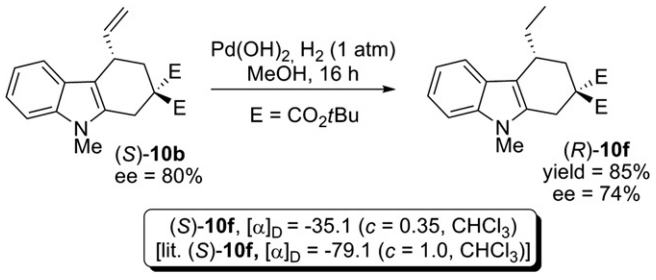
[a] All the reactions were carried out in anhydrous toluene, under nitrogen atmosphere (**L**/[Au]/[Ag]: 10/20/20 mol%). The catalytic complex was pre-formed in CH_2Cl_2 with [$AuCl(SMe_2)$].
[b] Isolated yield after flash chromatographic purification.
[c] Determined by HPLC analysis on a chiral column.
[d] At 0 °C, 48 h reaction time.



Scheme 4. Attempted gold-catalyzed synthesis of THGC derivatives.

a *hard* σ-base unit (hydroxyl group) adjacent in space, two possible coordination modes can be envisaged with dinuclear cationic gold complexes like **L10**-(Au_2OTf_2): a) *single-site interaction*, involving an Au/C=C bond interaction, and b) *chelating-like modality*, in which the mandatory Au/C=C interaction is accompanied by an additional contact involving the hydroxyl group and the second gold atom.

Preliminary insight into the activation mode came from the prominent role of the configuration of the C–C double bond over the chemical output (*vide infra*). This finding supports a direct engagement of the hydroxyl group in the catalytically active



Scheme 5. Determination of the absolute configuration of **10b**.

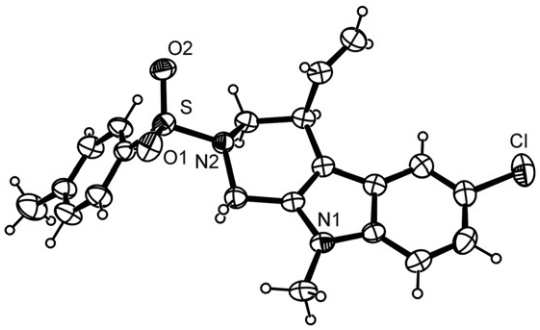


Fig. 3. ORTEP drawing of (*S*)-**12b**.

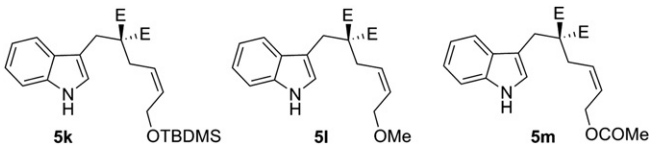
spatial arrangement between the indolyl-alcohols and dinuclear gold complex. Moreover, in a model cyclization process (**L10**-(Au_2Cl_2) 50 mol%) with the *O*-capped substrate (*Z*)-**5k** (*O*-TBDMS-**5a**), that would inhibit an effective Au–OH contact, the reaction rate was significantly lower (conv. 48%, ee = 56%, 24 h). Interestingly, the unreacted **5a** was recovered with complete inverted *E*-configuration of the double bond, that is ascribable to a gold-promoted auration/rotation/deauration event of the alkene function. It could be argued that the failure recorded with **5k** might be due to the presence of a sterically demanding silyl group in proximity of the allylic moiety, that would deny a competent electrophilic activation of the C–C double bond. However, even when more accessible indolyl methylether (*Z*)-**5l** was utilized as the substrate, the desired THC **9a** was isolated only in traces.

All these evidences emphasized the importance of the free OH function in controlling both the chemical and stereochemical courses of the process. Although a conclusive rational to this phenomena is not available yet, it is reasonable to assume the presence of a chelating arrangement of allylic framework over the dinuclear gold complex by means of bridging counterion effect (–OH···X···Au). However, the possibility that the second gold atom could act as a mere spectator, perhaps stabilizing the organogold intermediates through aurophilic interactions, cannot be ruled out at the present.

Finally, the complementarity of the [Au(I)]-catalyzed nucleophilic allylic substitution to the [Pd(0)/(II)] analogues, [6a] was demonstrated by synthesizing and subjecting to ring-closing event the indolyl acetate **5m** carrying an efficient leaving group at the allylic position. Interestingly, under optimal reaction parameters, **9a** was obtained only in poor extent (36% yield) and with synthetically unacceptable enantiomeric excess (15%, Scheme 6).

3. Conclusion

In conclusion, we have demonstrated the efficiency of (*Z*)-allylic alcohols as alkylating agents in the Au-catalyzed enantioselective FC-type reaction of indoles. The method exploits the



Scheme 6. Model substrates poorly reactive in the Au-catalyzed cyclization (E = CO_2Et).

unprecedentedly reported capability of chiral gold(I) catalysts to activate directly and selectively prochiral π-activated (*Z*)-allylic alcohols toward nucleophilic substitution in highly enantioselective manner. This methodology opens a route to enantiomerically enriched functionalized THBCs and THCs.

4. Experimental

4.1. General details

^{1}H NMR spectra were recorded on Varian 200 (200 MHz), Varian 400 (400 MHz) spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, bs = broad singlet, m = multiplet), coupling constants (Hz), number of protons. ^{13}C NMR spectra were recorded on a Varian 200 (50 MHz), Varian 400 (100 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). GC–MS spectra were taken by EI ionization at 70 eV on a Hewlett–Packard 5971 with GC injection. They are reported as: *m/z* (rel. intense). LC-electrospray ionization mass spectra were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. Chromatographic purification was done with 240–400 mesh silica gel. Analytical high performance liquid chromatography (HPLC) was performed on a liquid chromatograph equipped with a variable wave-length UV detector (deuterium lamp 190–600 nm), using Daicel Chiracel™ OD and AD columns (0.46 cm I.D. × 25 cm) (Daicel Inc). HPLC grade isopropanol and hexane were used as the eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 10 mm (Na_D line). Melting points were determined with Bibby Stuart Scientific Melting Point Apparatus SMP 3 and are not corrected. For analytic characterization of compounds **5a**–**k**, **6a**–**e**, **9a**–**i** and **10a**–**e** see Ref. [4]. The X-ray intensity data for **12b** were measured on a Bruker SMART Apex diffractometer equipped with a CCD area detector and a graphite monochromated Mo-Kα radiation source (λ = 0.71073 Å). Cell dimensions and the orientation matrix were initially determined from a least-squares refinement on reflections measured in three sets of 20 exposures, collected in three different ω regions, and eventually refined against all data. For all crystals, a full sphere of reciprocal space was scanned by 0.3° ω steps. The software SMART [23a] was used for collecting frames of data, indexing reflections and determination of lattice parameters. The collected frames were then processed for integration by software SAINT [23a] and an empirical absorption correction was applied with SADABS [23b]. The structure was solved by direct methods (SIR 97) [23c] and subsequent Fourier syntheses and refined by full-matrix least-squares calculations on F^2 (SHELXTL) [24] attributing anisotropic thermal parameters to the non-hydrogen atoms. All hydrogen atoms were located in the Fourier map. The aromatic, methyl, methylene and vinyl hydrogen atoms were placed in calculated positions, refined with isotropic thermal parameters $U(H) = 1.2\ U_{eq}$(C) or $U(H) = 1.5\ U_{eq}$(C-Me), and allowed to ride on their carrier carbons whereas the methine H atom was located in the Fourier map and refined isotropically [U(H) = 1.2 U_{eq}(C)]. Table 4.

Table 4
Crystal data and structure refinement for **12b**.

Compound	**12b**
Formula	$C_{21}H_{21}ClN_2O_2S$
M	400.91
T, K	296(2)
Crystal symmetry	Orthorhombic
Space group	$P2_12_12_1$
a, Å	7.969(2)
b, Å	10.659(4)
c, Å	23.880(6)
α, °	90
β, °	90
γ, °	90
V, Å^3	2028(1)
Z	4
D_c, Mg m^{-3}	1.313
μ(Mo-Kα), mm^{-1}	0.309
F(000)	840
Crystal size, mm	0.10 × 0.15 × 0.20
θ limits, °	2.09–23.40
Reflections collected	13,929
Unique obs. reflections [$F_o > 4\sigma(F_o)$]	2902 [R(int) = 0.0466]
Goodness-of-fit-on F^2	1.029
R_1 (F)[a], wR_2 (F^2)[b]	0.0346, 0.0801
Largest diff. peak and hole, e Å^{-3}	0.153 and −0.189

[a] $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$.
[b] $wR_2 = [\sum w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2]^{1/2}$ where $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ where $P = (F_o^2 + F_c^2)/3$.

4.2. General procedure for the synthesis of indole-methansulfonamides (**3a/4**)

To a solution of indole carboxaldehyde (2.4 mmol) in toluene (10 mL), tosyl amide (3.6 mmol) and $Ti(OEt)_4$ (4.8 mmol) were added and the mixture refluxed for 4 h. Then, after cooling at rt, the solvent was evaporated. The residue was dissolved in MeOH (10 mL) and THF (10 mL) and $NaBH_4$ (9.7 mmol) was slowly added at 0 °C. After 4 h stirring at room temperature, water (0.5 mL) was slowly added at 0 °C and the solvent was evaporated. Finally, the product was purified by flash column chromatography (SiO_2) to give the corresponding tosyl amide **3a/4**.

4.2.1. N-((1H-Indol-3-yl)methyl)-4-methylbenzenesulfonamide (**3a**)

Yield = 81%. Flash chromatography (*c*-Hex:AcOEt = 70:30); light red solid; m.p. = 151.4–152.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (bs, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.41 (m, 1H), 7.35 (m, 1H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.21 (ddd, *J* = 1.4 Hz, *J* = 7.2 Hz, *J* = 8.4 Hz, 1H), 7.09 (ddd, *J* = 1.1 Hz, *J* = 7.2 Hz, *J* = 8.0 Hz, 1H), 7.05 (m, 1H), 4.47 (*t*, *J* = 5.3 Hz, 1H), 4.34 (d, *J* = 5.3 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.4, 136.8, 136.2, 129.7 (2C), 127.5 (2C), 126.1, 123.3, 122.6, 120.0, 118.6, 111.3, 111.0, 40.0, 29.7, 21.3; MS (ES): *m/z* = 323.0 [M + Na]$^+$.

4.2.2 N-((1-Methyl-indol-2-yl)methyl-4-methyl-benzenesulfonamide (**4a**)

Yield = 79%. Flash chromatography (*c*-Hex:AcOEt = 70:30); white solid. m.p. = 146.3–147.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (dt, *J* = 1.6 Hz, *J* = 8.4 Hz, 2H), 7.52 (dt, *J* = 0.8 Hz, *J* = 8.0 Hz, 1H), 7.31 (dt, *J* = 1.6 Hz, *J* = 8.4 Hz, 1H), 7.28 (m, 1H), 7.23 (ddd, *J* = 1.2 Hz, *J* = 6.6 Hz, *J* = 9.2 Hz, 1H), 7.09 (ddd, *J* = 1.2 Hz, *J* = 6.6 Hz, *J* = 8.0 Hz, 1H), 6.31 (s, 1H), 4.53 (*t*, *J* = 6.0 Hz, 1H), 4.28 (d, *J* = 6.0 Hz, 2H), 3.71 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8, 138.0, 136.3, 133.3, 129.8 (2C), 127.1 (2C), 126.9, 122.1, 120.6, 119.7, 109.2, 102.4, 40.0, 29.8, 21.5; MS (ES): *m/z* = 315.0 [M + H]$^+$, 337.1 [M + Na]$^+$.

4.2.3. N-((5-Chloro-1-methyl-indol-2-yl)methyl)-4-methylbenzenesulfonamide (**4b**)

Yield = 68%. Flash chromatography (*c*-Hex:AcOEt = 70:30); white solid. m.p. = 130.5–131.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.8 Hz, 2H), 7.48 (m, 1H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.17

(m, 2H), 6.25 (s, 1H), 4.53 (d, $J = 7.1$ Hz, 1H), 4.21 (d, $J = 7.1$ Hz, 2H), 3.71 (s, 3H), 2.44 (s, 3H); MS (EI): m/z = 191 (100), 178 (42), 348 (38), 91 (36).

4.2.4. N-((1,5-Dimethyl-indol-2-yl)methyl)-4-methylbenzenesulfonamide (**4c**)

Yield = 79%. Flash chromatography (*c*-Hex:AcOEt = 70:30); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.80 (m, 3H), 7.31 (m, 2H), 7.16 (d, $J = 8.4$ Hz, 1H), 7.04 (dd, $J = 1.3$ Hz, $J = 8.4$ Hz, 1H), 6.21 (s, 1H), 4.64 (bs, 1H), 4.26 (d, $J = 6.1$ Hz, 2H), 3.68 (s, 3H), 2.44 (s, 3H), 2.42 (s, 3H); MS (EI): m/z = 171 (100), 158 (55), 91 (49), 328 (41), 144 (35), 207 (28).

4.2.5. N-((5-Methoxy-1-methy-indol-2-yl)methyl)-4-methylbenzenesulfonamide (**4d**)

Yield = 73%. Flash chromatography (*c*-Hex:AcOEt = 60:40); white solid. m.p. = 136.7–137.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, $J = 8.0$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 7.12 (d, $J = 9.0$ Hz, 1H), 6.95 (d, $J = 2.0$ Hz, 1H), 6.85 (dd, $J = 2.0$ Hz, $J = 9.0$ Hz, 1H), 6.19 (s, 1H), 4.68 (*t*, $J = 6.0$ Hz, 1H), 4.20 (d, $J = 6.0$ Hz, 2H), 3.81 (s, 3H), 3.62 (m, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1, 143.7, 136.2, 133.8, 133.3, 129.7, 127.2, 127.1, 112.3, 109.9, 102.2, 101.9, 55.8, 39.9, 29.8, 21.5; MS (ES): m/z = 345.0 $[M + H]^+$, 367.1 $[M + Na]^+$.

4.2.6. N-((1-Benzyl-indol-2-yl)methyl)-4-methylbenzenesulfonamide (**4e**)

Yield = 89%. Flash chromatography (*c*-Hex:AcOEt = 70:30); white solid. m.p. = 152.3–152.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, $J = 8.3$ Hz, 2H), 7.61 (d, $J = 7.7$ Hz, 1H), 7.27–7.31 (m, 6H), 7.23 (ddd, $J = 1.2$ Hz, $J = 8.2$ Hz, $J = 9.5$ Hz, 1H), 7.16 (ddd, $J = 1.2$ Hz, $J = 6.9$ Hz, $J = 7.8$ Hz, 1H), 6.94 (m, 2H), 6.40 (s, 1H), 5.33 (s, 2H), 4.66 (*t*, $J = 6.0$ Hz, 1H), 4.17 (d, $J = 6.0$ Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7, 137.8, 137.5, 136.1, 133.5, 129.7, 128.7, 127.5, 127.1,1, 25.9, 122.4, 120.7, 119.9, 109.7, 103.3, 46.4, 39.8, 21.5; MS (ES): m/z = 391.1 $[M + H]^+$, 413.0 $[M + Na]^+$.

4.2.7. N-((1-Allyl-indol-2-yl)methyl)-4-methylbenzenesulfonamide (**4f**)

Yield = 87%. Flash chromatography (*c*-Hex:AcOEt = 80:20); white solid. m.p. = 112.5–113.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, $J = 8.0$ Hz, 2H), 7.52 (d, $J = 7.5$ Hz, 1H), 7.21 (m, 2H), 7.10 (*t*, $J = 7.5$ Hz, 2H), 6.33 (s, 1H), 5.91 (m, 1H), 5.10 (d, $J = 10.1$ Hz, 1H), 4.71–4.82 (m, 4H), 4.22 (d, $J = 6.1$ Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7, 137.4, 136.2, 133.4, 133.3(2C), 133.2, 129.7 (2C), 127.1, 122.1, 120.6, 119.8, 116.3, 109.6, 102.9, 45.3, 39.7, 21.5; MS (ES): m/z = 341.0 $[M + H]^+$, 363.0 $[M + Na]^+$.

4.3. General procedure for N-allylic alkylation of tosyl amides **3/4** (**7/8**)

To a solution of **3** (0.3 mmol) in THF (3 mL), NaH (60% in mineral oil, 0.33 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. Then corresponding allyl bromide (*Z*)-**C** (0.36 mmol) was added and the reaction was stirred at reflux temperature overnight. Then, after cooling at rt, 5 mL of H_2O were added and the organic materials extracted with AcOEt (3 × 5 mL). The collected organic layers were washed with H_2O (6 × 5 mL), dried over Na_2SO_4 and concentrated to leave a yellow slurry. Flash column chromatography (SiO_2) eluting with a *c*Hex/ethyl acetate mixture.

Deprotection of the alcohol group: silyl-ether was dissolved in THF, then TBAF (1.5 eq. with respect to **3/4**) was added and the mixture was stirred for 4 h at room temperature. After that the solvents was evaporated to give a yellow slurry. Two-steps overall yields are given.

4.3.1. (Z)-**7a**

Yield = 45%. Flash chromatography (*c*-Hex:AcOEt = 70:30); white solid. m.p. = 128.7–129.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (bs, 1H), 7.80 (d, $J = 8.1$ Hz, 2H), 7.66 (d, $J = 8.1$ Hz, 1H), 7.38 (dt, $J = 0.8$ Hz, $J = 8.2$ Hz, 1H), 7.34 (d, $J = 8.1$ Hz, 1H), 7.22 (ddd, $J = 1.1$ Hz, $J = 7.0$ Hz, $J = 8.2$ Hz, 1H), 7.10 (ddd, $J = 1.1$ Hz, $J = 7.0$ Hz, $J = 8.0$ Hz, 1H), 7.02 (d, $J = 2.4$ Hz, 1H), 5.54 (m, 1H), 5.25 (m, 1H), 4.55 (s, 3H), 3.84 (*t*, $J = 5.6$ Hz, 1H), 3.82 (dd, $J = 1.4$ Hz, $J = 7.9$ Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.0, 143.4, 137.0, 131.6, 129.8 (2C), 127.4 (2C), 126.8, 124.3, 122.6, 120.0, 119.2, 111.3, 110.3, 108.7, 57.9, 43.1, 42.9, 21.5; MS (ES): m/z = 393.0 $[M + Na]^+$.

4.3.2. (Z)-**8a**

Yield = 68%. Flash chromatography (*c*-Hex:AcOEt = 70:30); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, $J = 7.7$ Hz, 2H), 7.55 (dt, $J = 0.9$ Hz, $J = 7.9$ Hz, 1H), 7.37 (d, $J = 7.7$ Hz, 2H), 7.35 (dd, $J = 0.9$ Hz, $J = 8.4$ Hz, 1H), 7.26 (ddd, $J = 1.1$ Hz, $J = 7.2$ Hz, $J = 8.4$ Hz, 1H), 7.12 (ddd, $J = 1.1$ Hz, $J = 7.1$ Hz, $J = 7.9$ Hz, 1H), 6.34 (s, 1H), 5.40 (m, 1H), 5.10 (m, 1H), 4.51 (s, 2H), 3.85 (s, 3H), 3.83 (m, 2H), 3.72 (dd, $J = 1.2$ Hz, $J = 6.8$ Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.9, 138.2, 135.6, 132.7, 131.4, 130.0, 129.7 (2C), 127.3 (2C), 126.7, 122.3, 120.3, 119.9, 109.4, 103.7, 57.9, 45.1, 43.7, 33.7, 21.5; MS (ES): m/z = 385.1 $[M + H]^+$, 407.0 $[M + Na]^+$.

4.3.3. (E)-**8a**

Yield = 64%. Flash chromatography (*c*-Hex:AcOEt = 70:30); white viscous wax. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, $J = 8.3$ Hz, 2H), 7.54 (d, $J = 8.1$ Hz, 1H), 7.36 (d, $J = 8.3$ Hz, 2H), 7.28–7.34 (m, 2H), 7.23 (ddd, $J = 1.4$ Hz, $J = 7.2$ Hz, $J = 9.2$ Hz, 1H), 7.11 (ddd, $J = 0.9$ Hz, $J = 7.2$ Hz, $J = 7.9$ Hz, 1H), 6.32 (s, 1H), 5.27 (m, 2H), 4.52 (s, 2H), 3.86 (s, 3H), 3.66–3.70 (m, 4H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8, 138.0, 135.9, 133.4, 132.8, 129.9, 127.4, 126.9, 127.4, 126.9, 125.4, 122.2, 120.5, 119.8, 109.2, 103.9, 62.6, 48.6, 44.8, 30.1, 21.6; MS (ES): m/z = 385.1 $[M + H]^+$, 407.0 $[M + Na]^+$.

4.3.4. (Z)-**8b**

Yield = 69%. Flash chromatography (*c*-Hex:AcOEt = 80:20); yellowish solid. m.p. = 139.6–140.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, $J = 8.0$ Hz, 2H), 7.50 (d, $J = 1.8$ Hz, 1H), 7.39 (d, $J = 8.0$ Hz, 2H), 7.25 (d, $J = 9.0$ Hz, 1H), 7.50 (dd, $J = 2.1$ Hz, $J = 9.0$ Hz, 1H), 6.28 (s, 1H), 5.45 (m, 1H), 5.04 (m, 1H), 4.47 (s, 1H), 3.89 (d, $J = 6.3$ Hz, 1H), 3.83 (s, 3H), 3.73 (d, $J = 7.3$ Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0, 136.6, 135.6, 134.1, 131.7, 130.0 (2C), 127.7, 127.3 (2C), 126.0, 125.5, 122.6, 119.7, 110.4, 103.2, 57.9, 44.9, 43.8, 30.3, 21.6; MS (ES): m/z = 419.0 $[M + H]^+$, 441.0 $[M + Na]^+$.

4.3.5. (Z)-**8c**

Yield = 62%. Flash chromatography (*c*-Hex:AcOEt = 80:20); Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, $J = 8.0$ Hz, 2H), 7.38 (d, $J = 8.0$ Hz, 2H), 7.32 (m, 1H), 7.23 (d, $J = 8.4$ Hz, 1H), 7.08 (d, $J = 8.4$ Hz, 1H), 6.25 (m, 1H), 5.38 (m, 1H), 5.11 (m, 1H), 4.47 (s, 2H), 3.83 (d, $J = 5.3$ Hz, 1H), 3.82 (s, 3H), 3.71 (dd, $J = 1.4$ Hz, $J = 7.2$ Hz, 1H), 2.48 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 136.6, 135.6, 132.6, 131.3, 129.9 (2C), 129.1, 127.4 (2C), 126.9, 126.2, 124.0, 119.9, 109.1, 103.1, 57.8, 45.2, 43.6, 30.1, 26.9, 21.3; MS (ES): m/z = 399.0 $[M + H]^+$, 421.1 $[M + Na]^+$.

4.3.6. (Z)-**8d**

Yield = 66%. Flash chromatography (*c*-Hex:AcOEt = 60:40); White wax. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, $J = 8.0$ Hz, 2H),

7.36 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 9.2 Hz, 1H), 9.98 (d, J = 2.4 Hz, 1H), 6.90 (dd, J = 1.8 Hz, J = 9.2 Hz, 1H), 6.25 (s, 1H), 5.38–5.43 (m, 1H), 5.06–5.11 (m, 1H), 4.45 (s, 3H), 3.85 (d, J = 7.2 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 2H), 3.71 (dd, J = 1.4 Hz, J = 6.4 Hz, 1H), 2.47 (s, 3H), 1.79 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.2, 143.8, 135.5, 133.5, 133.0, 131.4, 129.9 (2C), 129.6, 127.3 (2C), 126.9, 112.5, 110.1, 103.1, 101.9, 68,5, 57.8, 55.8, 45.0, 43.6, 27.7; MS (ES): m/z = 415 $[M + H]^+$, 437 $[M + Na]^+$.

4.3.7. (Z)-**8e**

Yield = 73%. Flash chromatography (*c*-Hex:AcOEt = 70:30); yellowish solid. m.p. = 71.6–72.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.3 Hz, 2H), 7.57 (dt, J = 0.8 Hz, J = 7.9 Hz, 1H), 7.23–7.29 (m, 6H), 7.19 (ddd, J = 1.4 Hz, J = 7.0 Hz, J = 9.4 Hz, 1H), 7.12 (ddd, J = 0.9 Hz, J = 7.0 Hz, J = 7.9 Hz, 1H), 7.00 (m, 2H), 4.06 (s, 1H), 5.5 (s, 2H), 5.44 (m, 1H), 5.09 (m, 1H), 4.39 (s, 2H), 3.87 (d, J = 6.8 Hz, 1H), 3.72 (d, J = 6.8 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7, 138.1, 137.6, 135.5, 132.5, 131.6, 129.8 (2C), 128.6, 127.3 (2C), 127.1, 127.0, 126.1, 125.9, 122.5, 120.4, 120.0, 110.0, 104.7, 104.6, 57.7, 46.4, 44.6, 43.6, 21.5; MS (ES): m/z = 461.1 $[M + H]^+$, 483.0 $[M + Na]^+$.

4.3.8. (Z)-**8f**

Yield = 74%. Flash chromatography (*c*-Hex:AcOEt = 70:30); yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, J = 8.2 Hz, 2H), 7.55 (dt, J = 1.0 Hz, J = 7.9 Hz, 1H), 7.37 (d, J = 8.2 Hz, 2H), 7.33 (ddd, J = 0.8 Hz, J = 1.8 Hz, J = 8.3 Hz, 1H), 7.23 (ddd, J = 1.1 Hz, J = 7.0 Hz, J = 8.2 Hz, 1H), 7.11 (ddd, J = 1.1 Hz, J = 7.0 Hz, J = 7.9 Hz, 1H), 6.37 (s, 1H), 6.00 (m, 1H), 5.77 (m, 1H), 5.11 (m, 2H), 4.92 (m, 3H), 4.45 (s, 2H), 3.90 (m, 2H), 3.75 (d, J = 7.0 Hz, 2H), 2.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7, 137.6, 135.6, 133.3, 131.6, 129.8 (2C), 127.3, 126.9 (2C), 126.8, 122.2, 120.3, 119.8, 116.2, 109.8, 107.7, 104.2, 57.7, 45.4, 44.4, 43.5, 21.4; MS (ES): m/z = 411.1 $[M + H]^+$, 433.0 $[M + Na]^+$.

4.3.9. (Z)-**5l**

Synthesized through procedure 4.3, employing indolyl malonate **1** and (*Z*)-1-MsO-4-methoxybut-2-ene.[25a] Yield = 56%. Flash chromatography (*c*-Hex:AcOEt = 80:20); light brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (bs, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.11–7.17 (m, 2H), 7.00 (bs, 1H), 5.67 (m, 2H), 4.15 (d, J = 7.6 Hz, 4H), 3.89 (d, J = 5.6 Hz, 2H), 3.45 (s, 2H), 3.28 (s, 3H), 2.72 (d, J = 6.8 Hz, 2H), 1.22 (*t*, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 135.8, 129.9, 128.2, 126.6, 123.1, 123.0, 122.0, 119.4, 111.0, 110.0, 68.2, 61.3, 58.4, 53.0, 30.7, 27.9, 13.9; MS (ES): m/z = 374.1 $[M + H]^+$.

4.3.10. (Z)-**5m**

Synthesized through procedure 4.3, employing indolyl malonate **1** and (*Z*)-4-bromobut-2-enyl acetate.[25b] Yield = 58%. Flash chromatography (*c*-Hex:AcOEt = 75:25); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (bs, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.07–7.17 (m, 2H), 6.98 (d, J = 2.4 Hz, 1H), 5.69 (m, 2H), 4.52 (d, J = 5.1 Hz, 2H), 4.14 (d, J = 7.1 Hz, 4H), 3.44 (s, 2H), 2.73 (d, J = 5.9 Hz, 2H), 2.02 (s, 3H), 1.21 (*t*, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 135.8, 128.4, 128.1, 127.1, 123.1, 123.0, 121.9, 119.3, 118.7, 11.0, 109.8, 61.2, 60.3, 58.4, 30.7, 30.6, 28.0, 13.9; MS (ES): m/z = 402.2 $[M + H]^+$.

4.4. Detemination of the absolute configuration of **10b**

The vinyl-carbazole (*S*)-**10b** (ee: 80%, 0.10 mmol) was added to a suspension of $Pd(OH)_2$ (20 mol%) in anhydrous MeOH (4 mL). The apparatus was connected to a balloon filled with hydrogen in order to maintain a reducing atmosphere (≈1 atm). The dark mixture was stirred at room temperature overnight. Then the insoluble black powder was filtered off (CAUTION!) with celite, washed with CH_2Cl_2 (10 mL) and the organics evaporated under reduced pressure. The crude (*R*)-**10f** was finally purified by flash chromatography (*c*-Hex: AcOEt = 8:2). Yield = 85%. *Ee* = 74%. $[\alpha]_D$ = −35.1 (c = 0.35, $CHCl_3$), [lit. (*R*)-**10f**, *ee* = 88%, $[\alpha]_D$ = −79.1 (c = 1.0, $CHCl_3$)]. See ref. [4] for analytical details.

4.5. Representative procedure for the enantioselective gold-catalyzed synthesis of tetrahydro-β-carbolines **12**

A flamed two-neck round bottom flask, under nitrogen atmosphere, was charged with 1 mL of anhydrous CH_2Cl_2, 6.2 mg of **L10** (5.6 μmol) and 3.2 mg of [AuCl(DMS)] (11.2 μmol). The mixture was stirred for 30 min at rt, then the solvent removed in vacuum and replaced with anhydrous toluene (1 mL). After covering the flask with an aluminum foil, 2.8 mg of AgOTf (11.2 μmol) were added and the mixture led to stir for 30 min, the desired alcohol **8** (56 μmol) was added and the mixture stirred for the desired time (24–48 h) in the dark. Evaporation of the volatiles led to a crude mixture that was directly charged into a flash chromatographic column for purification.

4.5.1. (S)-9-Methyl-2-tosyl-4-vinyl-2,3,4,9-tetrahydro-pyrido[3,4-b]indole **12a**

Yield = 75%. ee = 80%. Flash chromatography (*c*-Hex:AcOEt = 90:10); white solid. m.p. = 171.0–172.0 °C; $[\alpha]_D$ = +5.0 (c = 0.8, $CHCl_3$). HPLC analysis: OD column (225 nm), 40 °C, method: *n*-Hex:IPA = 80:20, flow 1.0 mL/min, $t_{(R)}$ = 10.3 min, $t_{(S)}$ = 11.8 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.24 (dt, J = 0.9 Hz, J = 8.2 Hz, 1H), 7.16 (ddd, J = 1.2 Hz, J = 7.2 Hz, J = 8.3 Hz, 1H), 7.04 (ddd, J = 0.9 Hz, J = 7.2 Hz, J = 8.0 Hz, 1H), 5.87 (ddd, J = 8.0 Hz, J = 10.0 Hz, J = 17.1 Hz, 1H), 5.22 (m, 2H), 4.32 (d, J = 14.1 Hz, 1H), 4.29 (d, J = 14.1 Hz, 1H), 3.75 (m, 1H), 3.59 (s, 3H), 3.45 (dd, J = 4.6 Hz, J = 11.8 Hz, 1H), 3.87 (dd, J = 6.0 Hz, J = 11.8 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8, 138.3, 137.3, 133.7, 130.1, 129.8 (2C), 127.7 (2C), 126.0, 121.5, 119.3, 119.1, 116.8, 108.9, 108.8, 49.4, 42.8, 38.2, 31.9, 29.5; MS (ES): m/z = 367.1 $[M + H]^+$, 389.0 $[M + Na]^+$.

4.5.2. (S)-6-Chloro-9-methyl-2-tosyl-4-vinyl-2,3,4,9-tetrahydro-pyrido[3,4-b]indole **12b**

Yield = 93%. Ee = 79%. Flash chromatography (*c*-Hex:AcOEt = 90:10); Yellow wax. $[\alpha]_D$ = +3 (c = 1.2, $CHCl_3$). HPLC analysis: AD column (214 nm), 40 °C, method: *n*-Hex:IPA = 80:20, flow 1.0 mL/min, $t_{(R)}$ = 12.8 min, $t_{(R)}$ = 16.6 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.8 Hz, 1H), 7.13 (dd, J = 1.6 Hz, J = 8.8 Hz, 1H), 5.85 (ddd, J = 8.0 Hz, J = 10.0 Hz, J = 17.2 Hz, 1H), 5.26 (m, 2H), 4.33 (d, J = 15.1 Hz, Hz, 1H), 4.27 (d, J = 15.1 Hz, 1H), 3.71 (m, 1H), 3.60 (s, 3H), 3.48 (dd, J = 5.1 Hz, J = 11.9 Hz, 1H), 3.20 (dd, J = 6.4 Hz, J = 11.9 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.9, 137.8, 135.9, 135.7, 133.5, 131.6, 130.2, 129.8 (2C), 127.8 (2C), 125.1, 121.4, 118.6, 109.8, 108.6, 49.3, 42.7, 38.1, 26.9, 26.7; MS (ES): m/z = 401.0 $[M + H]^+$, 433.0 $[M + Na]^+$.

4.5.3. (S)-6,9-Dimethyl-2-tosyl-4-vinyl-2,3,4,9-tetrahydro-pyrido[3,4-b]indole **12c**

Yield = 75%. Ee = 80%. Flash chromatography (*c*-Hex:AcOEt = 90:10); White solid. m.p. = 171.4–171.9 °C; $[\alpha]_D$ = +2 (c = 0.8, $CHCl_3$). HPLC analysis: AD column (214 nm), 40 °C, method: *n*-Hex:IPA = 80:20, flow 0.7 mL/min, $t_{(S)}$ = 12.2 min, $t_{(R)}$ = 14.1 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 7.28 (m, 1H), 7.15 (d, J = 8.2 Hz, 1H), 7.01 (dd, J = 1.4 Hz, J = 8.3 Hz, 1H), 5.90 (ddd, J = 7.9 Hz, J = 10.9 Hz,

J = 17.1 Hz, 1H), 5.25 (m, 2H), 4.34 (dd, J = 1.4 Hz, J = 14.5 Hz, 1H), 4.27 (dd, J = 1.4 Hz, J = 14.5 Hz, 1H), 3.76 (m, 1H), 3.59 (s, 3H), 3.44 (dd, J = 4.7 Hz, J = 11.7 Hz, 1H), 3.27 (dd, J = 5.9 Hz, J = 11.7 Hz, 1H), 2.44 (s, 3H), 2.42 (s, 3H); ^{13}C- NMR (100 MHz, $CDCl_3$): δ = 143.8, 138.5, 135.7, 133.7, 130.1, 129.8 (2C), 128.6, 127.6 (2C), 126.2, 123.0, 118.7, 116.7, 108.5, 108.3, 49.4, 42.8, 38.1, 29.5, 21.5, 21.4; MS (ES): m/z = 381.2 $[M + H]^+$, 403.1 $[M + Na]^+$.

4.5.4. (S)-6-Methoxy-9-methyl-2-tosyl-4-vinyl-2,3,4,9-tetrahydro-pyrido[3,4-b]indole **12d**

Yield = 61%. Ee = 76%. Flash chromatography (*c*-Hex:AcOEt = 85:15); white solid; m.p. = 136–165 °C; $[\alpha]_D = +7.6$ (c = 0.5, $CHCl_3$). HPLC analysis: OD column (214 nm), 40 °C, method: *n*-Hex:IPA = 85:15, flow 1.0 mL/min, $t_{(R)}$ = 12.4 min, $t_{(S)}$ = 13.8 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 9.2 Hz, 1H), 6.96 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 2.4 Hz, J = 9.2 Hz, 1H), 5.84–5.93 (m, 1H), 5.30 (dt, J = 1.6 Hz, J = 16.8 Hz, 1H), 5.20 (dd, J = 2.4 Hz, J = 10.8 Hz, 1H), 4.29 (s, 2H), 3.82 (s, 3H), 3.70–3.75 (m, 1H), 3.59 (s, 3H), 3.50 (dd, J = 5.2 Hz, J = 12.4 Hz, 1H), 2.23 (dd, J = 7.2 Hz, J = 12.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.8, 143.8, 138.3, 133.7, 132.6, 130.7, 129.8 (2C), 127.6 (2C), 126.4, 116.7, 111.1, 109.4, 108.3, 101.5, 55.9, 49.4, 42.8, 38.2, 31.9, 26.9; MS (ES): m/z = 397.1 $[M + H]^+$.

4.5.5. (S)-9-Benzyl-2-tosyl-4-vinyl-2,3,4,9-tetrahydro-pyrido[3,4-b]indole **12e**

Yield = 95%. Ee = 70%. Flash chromatography (*c*-Hex:AcOEt = 95:5). Light brown oil. $[\alpha]_D = -4$ (c = 1.1, $CHCl_3$). HPLC analysis: OD column (214 nm), 40 °C, method: *n*-Hex:IPA = 80:20, flow 0.7 mL/min, $t_{(S)}$ = 14.7 min, $t_{(R)}$ = 17.4 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.4 Hz, 1H), 7.23–7.29 (m, 7H), 7.15 (ddd, J = 1.3 Hz, J = 8.3 Hz, J = 9.1 Hz, 1H), 7.08 (ddd, J = 1.3 Hz, J = 6.9 Hz, J = 7.3 Hz, 1H), 7.00 (m, 2H), 5.92 (m, 1H), 5.25–5.32 (m, 2H), 5.22 (s, 2H), 4.22 (s, 2H), 3.79 (m, 1H), 3.48 (d, J = 6.8 Hz, 1H), 3.25 (d, J = 6.8 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7, 139.3, 137.1, 136.9, 133.8, 133.2, 130.1, 129.7 (2C), 128.9 (2C), 127.6, 127.6 (2C), 126.2 (2C), 125.9, 121.8, 119.5, 119.2, 109.6, 109.4, 49.3, 46.8, 42.8, 38.2, 26.9; MS (ES): m/z = 461.1 $[M + H]^+$, 483.0 $[M + Na]^+$.

4.5.6. (S)-9-Allyl-2-tosyl-4-vinyl-2,3,4,9-tetrahydro-pyrido[3,4-b]indole **12f**

Yield = 71%. Ee = 78%. Flash chromatography (*c*-Hex:AcOEt = 90:10). White sticky solid. $[\alpha]_D = +1.2$ (c = 1.3, $CHCl_3$). HPLC analysis: OD column (210 nm), 40 °C, method: *n*-Hex:IPA = 80:20, flow 1.0 mL/min, $t_{(R)}$ = 7.6 min, $t_{(S)}$ = 11.1 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.1 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.1 Hz, 1H), 7.17 (ddd, J = 1.4 Hz, J = 7.2 Hz, J = 8.3 Hz, 1H), 7.07 (ddd, J = 1.4 Hz, J = 7.2 Hz, J = 7.9 Hz, 1H), 5.90 (m, 2H), 5.31 (m, 1H), 5.20 (m, 1H), 5.14 (ddd, J = 1.6 Hz, J = 2.6 Hz, J = 10.3 Hz, 1H), 4.87 (ddd, J = 1.7 Hz, J = 2.7 Hz, J = 17.7 Hz, 1H), 4.62 (m, 2H), 4.30 (s, 2H), 3.78 (m, 1H), 3.49 (dd, J = 4.7 Hz, J = 11.8 Hz, 1H), 3.26 (dd, J = 6.1 Hz, J = 11.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8, 138.3, 136.8, 133.9, 132.8, 129.9 (2C), 129.8, 127.9 (2C), 127.6, 126.2, 121.6, 119.4, 119.2, 116.8, 109.4, 109.2, 49.3, 45.6, 42.6, 38.1, 29.7; MS (ES): m/z = 393.1 $[M + H]^+$, 415.0 $[M + Na]^+$.

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Appendix A. Supplementary material

CCDC 794470 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.

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