VIP Alkylation

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Enantioselective Gold-Catalyzed Allylic Alkylation of Indoles with Alcohols: An Efficient Route to Functionalized Tetrahydrocarbazoles**

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The use of π-activated alcohols[1] in catalytic Friedel–Crafts alkylation (FCA) reactions has become a well-known and eco-sustainable reality.[2] A large number of Lewis and Brønsted–Lowry acid catalyzed benzylation/allylation/propargylation procedures has been documented, and they allow rapid access to structural complexity in the realm of aromatic compounds. Despite efficiency, the formation of positively charged intermediates in FCA with alcohols (S_N1-type mechanism) makes the stereocontrol of the process a challenging task that has not yet been overcome.[3] As a matter of fact, at present only a handful of reports addressing such an issue have been documented.[4–6]

As a part of our program directed toward the development of innovative catalytic and stereoselective methodologies for the synthesis of polycyclic aromatic compounds,[7] we describe herein the first example of direct activation of allylic alcohols[8] in enantioselective catalytic Friedel–Crafts allylic alkylations[9] of indoles.[10] The methodology allows 1-vinyl- and 4-vinyltetrahydrocarbazoles (THCs)[11] to be readily prepared in a highly enantioselective manner.

Our working hypothesis deals with the choice of a suitable chiral Lewis acid promoter, which is capable of efficiently activating the hydroxy group as a leaving group without the formation of an allylic carbocationic species (S_N1-type mechanism) that would preclude any stereochemical control in the course of the reaction.

Guidelines for searching for a suitable catalyst came from the intrinsic "chelating" architecture of the allylic alcohol featuring a soft π-base center (C=C bond) and a hard σ-base unit (hydroxy group) that are adjacent to each other.[12] Cationic late-transition-metal complexes (e.g. Pt, Ag, Au),[13] which feature dual function (i.e. σ- and π-acidity), appeared suitable candidates to obtain conformationally rigid adducts between the FC precursors and the catalyst. In this context, chelating (monometallic catalyst) or single-point (bimetallic catalyst) interactions were envisioned (Figure 1).[14]

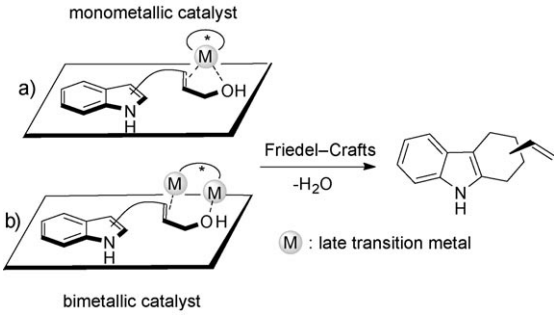

Figure 1. Working hypothesis for the stereoselective metal-catalyzed Friedel–Crafts allylic alkylation of indoles with allylic alcohols.

In an effort to develop a catalytic methodology tolerant of challenging N1-unprotected indoles, the specifically designed indolyl alcohol (*Z*)-**1a** was synthesized in two steps starting from readily available indolyl malonate[15] (see the Supporting Information and Table 1).

Chiral bis(phosphine)–platinum(II)[16a,d,17] and chiral bimetallic gold(I) complexes of the general formula [(P-P)Au_2X_2] (P-P = **L1**–**L12**; Figure 2),[16c,18–20] were taken into consideration as leading examples of mono- and bimetallic catalysts, respectively. Here, while Pt-based catalysts promoted the formation of **2a** to a good extent but always in racemic form (see Table SI in the Supporting Information), chiral gold(I) complexes provided promising results in terms of chemical yield and enantiomeric excess. The results obtained with a range of [(P-P)Au_2Cl_2] complexes are reported in Table 1.

Good to high yields of the isolated products were obtained (66–96%; except for **L5**, see Table 1, entry 5) in toluene as the solvent. In terms of stereoinduction, (*S*)-3,5-*t*Bu_2-4-MeO-MeOBiphep **L10** furnished the best results and led to **2a** in 78% yield and 88% *ee* after 24 hours reaction time (Table 1, entry 10).

The nature of the counterion proved to be crucial for both reaction rate and stereoinduction, with OTf^- (trifluoromethanesulfonate) acting as the best counterion (Table 1,

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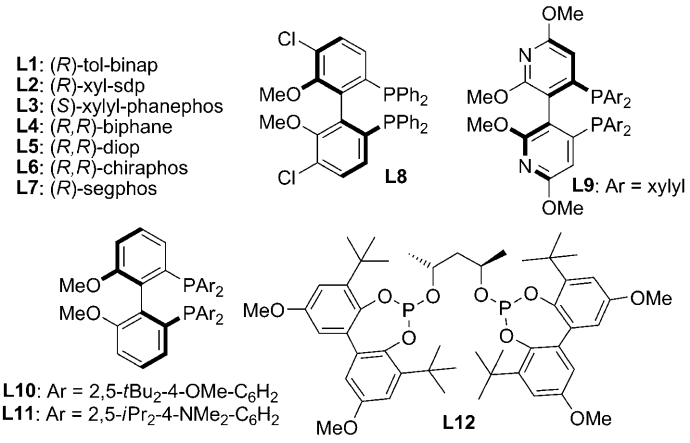
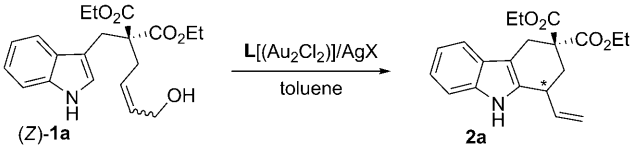


Figure 2. Library of chiral bidentate ligands screened in the gold-catalyzed enantioselective alkylation of indole with allylic alcohols. (*R*)-tol-binap = (*R*)-(+)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl, (*R*,*R*)-binaphane = (*R*,*R*)-1,2-bis[(*R*)-4,5-dihydro-3*H*-binaphtho(1,2-*c*:2′,1′-*e*)phosphino]benzene, (*R*,*R*)-chiraphos = (2*R*,3*R*)-(+)-2,3-bis(diphenylphosphino)butane, (*R*,*R*)-diop = (4*R*,5*R*)-4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane, (*S*)-xylyl-phanephos = (*S*)-(+)-4,12-bis[di(3,5-xylyl)phosphino]-[2.2]paracyclophane(*R*)-xyl-sdp = (*R*)-(+)-7,7′-bis[di(3,5-dimethylphenyl)phosphino]-2,2′,3,3′-tetrahydro-1,1′-spirobiindane, (*R*)-segphos = (*R*)-(+)-5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole.

Table 1: Optimization of the reaction conditions for the intramolecular asymmetric allylic alkylation of **1a**.[a]



Entry	L/AgX	*t*/*T* [h/°C]	Yield [%][b]	*ee* [%][c]
1	**L1**/AgOTf	24/RT	72	30
2	**L2**/AgOTf	24/RT	85	9
3	**L3**/AgOTf	24/RT	90	28
4	**L4**/AgOTf	24/RT	95	29
5	**L5**/AgOTf	24/RT	8	0
6	**L6**/AgOTf	24/RT	95	0
7	**L7**/AgOTf	24/RT	95	72
8	**L8**/AgOTf	24/RT	77	35
9	**L9**/AgOTf	24/RT	73	48
10	(*R*)-**L10**/AgOTf	24/RT	78	88
11	**L11**/AgOTf	24/RT	66	22
12	**L12**/AgOTf	24/RT	96	6
13	(*R*)-**L10**/$AgBF_4$	24/RT	55	87
14	(*R*)-**L10**/$AgSbF_6$	24/RT	25	62
15	(*R*)-**L10**/AgOTs	24/RT	10	92
16	(*R*)-**L10**/$AgNTf_2$	24/RT	95	65
17	(*R*)-**L10**/AgOTf	48/0	95	90
18[d]	(*R*)-**L10**/AgOTf	64/0	71	84
19[e]	(*S*)-**L10**/AgOTf	48/0	84	90
20[f]	(*S*)-**L10**/AgOTf	48/0	55	92
21[g]	(*R*)-**L10**/AgOTf	48/0	27	94

[a] All the reactions were carried out in anhydrous toluene under a nitrogen atmosphere. **L**/[Au]/[Ag] = 10:20:20 mol%, unless otherwise specified. The catalytic complex was synthesized in situ in CH_2Cl_2 with $AuCl{\cdot}SMe_2$. [b] Yield of isolated product after purification by flash chromatography. [c] Determined by HPLC on a chiral stationary phase. [d] At 0°C, 64 h, **L10**/[Au]/[Ag] = 5:10:10 mol%. [e] Preformed **L10**-(Au_2Cl_2) complex was employed. Opposite stereoinduction with respect to entry 15 was detected. [f] In the presence of molecular sieves (4 Å). [g] The reaction was carried out without any moisture restriction (reagent grade toluene, no air exclusion).

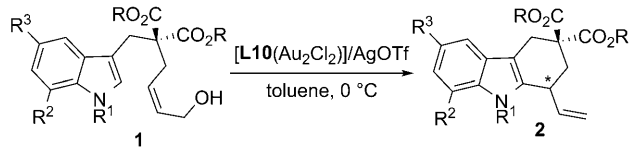
entries 10, 13–16). By lowering the reaction temperature to 0°C the enantiomeric excess increased to 90% with 95% yield after 48 hours, (Table 1, entry 17). Preformed[16c,21] or in situ assembled **L10**–(Au_2Cl_2) complexes furnished comparable outcomes (compare Table 1, entry 17 with 19), and rigorous moisture exclusion was required to achieve synthetically acceptable reaction rates (Table 1, entry 21). However, the addition of activated molecular sieves did not markedly affect the stereochemical outcome of the process (Table 1, entry 20). Further experimental controls were carried out to rationalize the role of silver in the reaction course. Firstly, removal of the insoluble AgCl from the reaction mixture did not lead to significant variations with respect to entry 17 in Table 1, and secondly, the inertness of the **L10**–(Ag_2OTf_2) complex in the model cyclization was proven by running the reaction in the absence of $AuCl{\cdot}SMe_2$ (only traces of **2a** were observed). To the best of our knowledge, this is among the few examples of enantioselective gold(I)-catalyzed transformations of an unactivated C=C bonds.[22,23]

Having established the optimal reaction conditions, we explored the scope of the methodology by subjecting a range of indolyl alcohols **1b–j** to ring-closing Friedel–Crafts alkylation and the results are shown in Table 2.

Tolerance toward a wide range of functional groups (electron-withdrawing and -donating groups) on the indolyl unit was demonstrated by obtaining the corresponding tetrahydrocarbazoles (**2**) in good yields and high enantiomeric excesses (up to 96%; Table 2, entries 1–5, 10, 11). Notably, precursor **1g** (Table 2, entry 7) did not undergo ring-closing Friedel–Crafts alkylation, probably owing to detrimental steric hindrance of the methyl group near the cyclization site (C2-position). In the same manner, the role of the R group of the malonate tethering unit was analyzed (Table 2, entries 8 and 9) by replacing the model (diethyl)indolyl alcohol **1a** with the corresponding (dimethyl) (**1h**) and (di*t*Bu) precursors (**1i**). Interestingly, even though the presence of bulky *tert*-butyl groups positively affected the enantiomeric excess (92% *ee*; Table 2, entry 9), the smaller methyl substituent caused a slight drop in enantiodifferentiation (85% *ee*; Table 2, entry 8).

Moreover, the methodology proved to be a reliable synthetic alternative to the intramolecular hydroarylation of allenes,[16b,c] which have been reported by Widenhoefer and co-workers for the synthesis of enantiomerically enriched 4-vinyl-THCs (**4**). As a proof of concept, readily accessible indolyl alcohols **3a–e** (see the Supporting Information for synthetic details) were subjected to gold-catalyzed intramolecular FCA under the optimum reaction conditions leading to the corresponding polycyclic compounds **4a–e** in good to high enantiomeric excesses (up to 86% *ee*, Table 3).

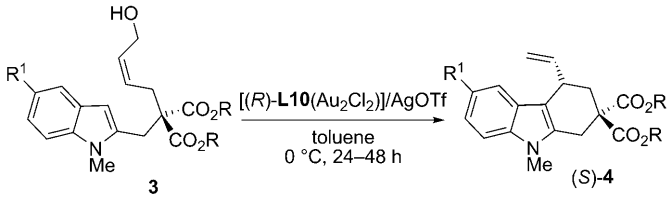
Table 2: Catalytic enantioselective intramolecular Friedel–Crafts alkylation studies for the synthesis of 1-vinyl-tetrahydrocarbazoles **2**.[a]



Entry	Alcohol	$R/R^1/R^2/R^3$	t [h]	Yield [%][b]	*ee* [%][c]
1[d]	**1b**	Et/H/H/Br	48	60	86
2	**1c**	Et/H/H/Me	24	68	92
3[d]	**1d**	Et/H/H/OMe	24	79	84
4	**1d**	Et/H/H/OMe	48	55	96
5	**1e**	Et/H/Me/H	48	91	83
6[d]	**1f**	Et/H/H/Cl	48	52	85
7	**1g**	Et/Me/H/H	48	–	–[e]
8	**1h**	Me/H/H/H	24	74	85
9	**1i**	*t*Bu/H/H/H	48	53	92
10[d]	**1j**	Et/H/H/OBn	24	78	80
11	**1j**	Et/H/H/OBn	48	69	82

[a] All the reactions were carried out in anhydrous toluene under a nitrogen atmosphere. **L10**/[Au]/[Ag] = 10:20:20 mol%, unless otherwise specified. The catalytic complex was synthesized in situ in CH_2Cl_2 with $AuCl{\cdot}SMe_2$. [b] Yield of isolated product after purification by flash chromatography. [c] Determined by HPLC on a chiral stationary phase. [d] Room temperature. [e] Unchanged **1g** was recovered (80%). Bn = benzyl.

Table 3: Catalytic enantioselective intramolecular Friedel–Crafts alkylation studies for the synthesis of 4-vinyl-tetrahydrocarbazoles **4**.[a]



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

[a] All the reactions were carried out in anhydrous toluene under a nitrogen atmosphere. **L10**/[Au]/[Ag] = 10:20:20 mol%, unless otherwise specified. The catalytic complex was synthesized in situ in CH_2Cl_2 with $AuCl{\cdot}SMe_2$. [b] Yield of isolated product after purification by flash chromatography. [c] Determined by HPLC on a chiral stationary phase. The absolute configuration for **4b** was determined by chemical correlation with a known compound.[17d] The absolute configuration for **4a**,**c–e** was assigned by analogy. [d] Room temperature.

To shed light on the active coordination mode of the bimetallic gold complex to the indolyl alcohols **1**, some control experiments were carried out. We decided to investigate stepwise the role of both the C=C bond and the hydroxy group in the activation/discrimination of stereochemistry events of the catalytic cycle.[24]

The participation of the C=C bond in the gold activation of the substrate was established by subjecting (*E*)-**1a** to cyclization under the optimum reaction conditions. In this case, the expected π-(C=C)–Au interaction would generate a diastereomeric gold(I)–π complex of **1a** with respect to (*Z*)-**1a**, with consequent effects on the chemical output and enantiomeric excess. Interestingly, (*E*)-**1a** was completely inert toward the cyclization conditions (see the Supporting Information), and this finding could be rationalized in terms of an unfavorable spatial arrangement of the sterically demanding bimetallic catalyst on the *trans* allylic alcohol moiety. Such evidence invokes a substrate-controlled mechanism, which is analogous to the gold-catalyzed hydroindolination of allenes.[16b]

Next, insight into the direct activation of the hydroxy group by the gold complex was obtained by running a control experiment with (*Z*)-*O*-TBDMS-**1a** (**1a′**) that would inhibit an effective and direct Au–O interaction (**L10**–(Au_2Cl_2) 50 mol%). Notably, the ring-closing event was significantly slowed down (48% conv., 56% *ee*) and complete inversion of the C=C bond configuration ($Z \rightarrow E$) of the remaining **1a** occurred (see the Supporting Information). Such evidence can be ascribed to a gold-promoted auration/rotation/deauration event of the C=C bond. This event becomes predominant respective to the FC process when direct gold-activation of the hydroxy group is denied.

Although such evidence cannot be considered conclusive to support an operating bimetallic activation, a speculative outer-sphere[25,26] mechanism that considers simultaneous C=C/OH activation is represented in Figure 3, left cycle. Here, the initial catalyst–substrate aggregate **I** undergoes an intramolecular FCA to generate the Wheland-type intermediate **II**. After rearomatization of the indolyl core, one equivalent of TfOH is released which could be involved in restoring the catalytically active cationic gold complex and consequent formation of **2**. However, at present an analogous mechanistic pathway involving monometallic gold-activation and Brønsted acid assisted β-hydroxy elimination cannot be ruled out (Figure 3, right cycle).[27]

Different to what commonly occurs in the gold-catalyzed hydroarylations of allenes, a final proton-deauration event is not operating here, and the Brønsted acid present in solution seems to act as a scavenger for the hydroxy groups. This proposal is supported by the fact that while in allene chemistry the addition of bases completely suppresses the catalytic cycle,[28] in our model reaction ((*Z*)-**1a**, **L10**–(Au_2Cl_2)/AgOTf, RT) the use of noncoordinating 2,6-di-*tert*-butylpyridine (30 mol%) simply caused a drop in the reaction rate (25% conv., 20 h) because of the formation of less acidic pyridium salt, with almost unvaried levels of stereoinduction (90% *ee*).

In conclusion, we have developed the first example of direct catalytic enantioselective Friedel–Crafts allylic alkylation reaction with alcohols.[4] This method exploits the unprecedented capability of chiral gold(I) catalysts to activate selectively prochiral π-activated alcohols toward aromatic functionalization in a highly enantioselective manner. Current efforts are directed to the use of such a protocol in the synthesis of polycyclic indolyl-containing natural compounds.

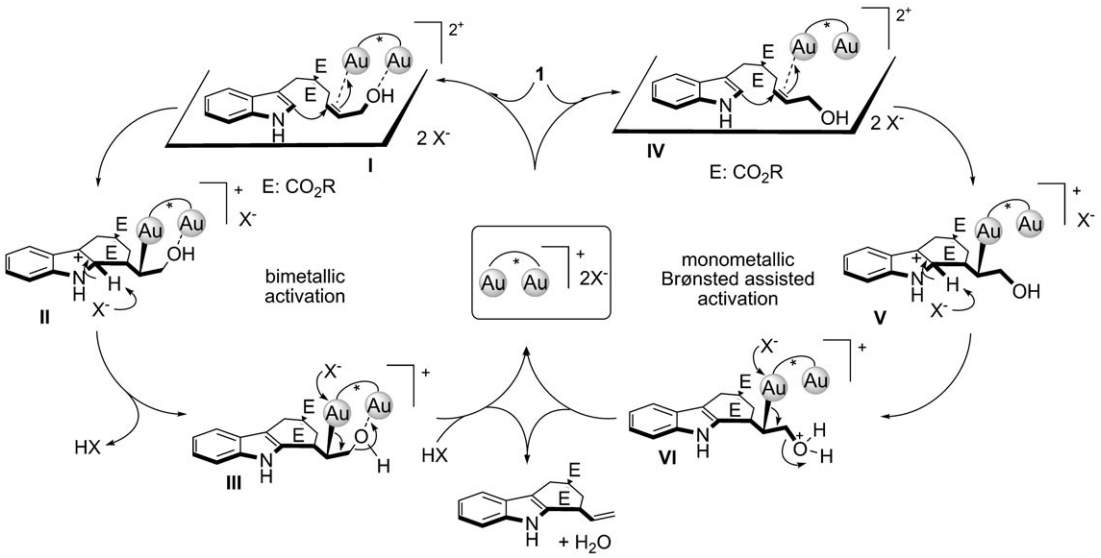


Figure 3. Tentative mechanism (case of 1-vinyl-THCs) for the enantioselective gold-catalyzed alkylation of indoles with allylic alcohols.

Moreover, extension of the present stereoselective gold-catalyzed allylic alkylation to different molecular architectures is underway.

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