Gold(I)-catalyzed enantioselective synthesis of tetrahydrocarbazoles through dearomative [4+2] cycloadditions of 3/2-substituted 2/3-vinylindoles

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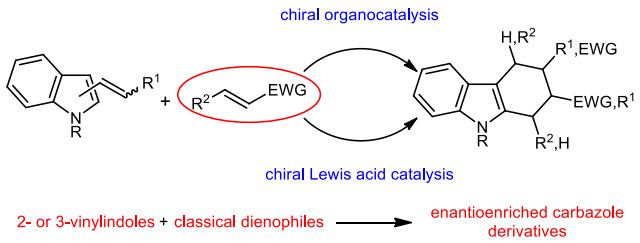
Abstract. The gold-catalyzed synthesis of tetrahydrocarbazoles through dearomative [4+2] cycloaddition reactions of 3/2-substituted 2/3-vinylindoles with allenamides is reported. In particular, we optimized the enantioselective variant of these cycloadditions. Using allenamides as dienophiles 3-substituted-2-vinyl indoles gave the corresponding carbazoles with high chemo-, regio- and enantioselectivity. Good results were obtained also with 2-methyl-3-vinylindoles even if mixture of (*Z*) and (*E*) isomers were isolated in high *e.r.* and in excellent overall yields.

Keywords: vinylindole; allenamide; [4+2] cycloadditions; gold; asymmetric catalysis

Introduction

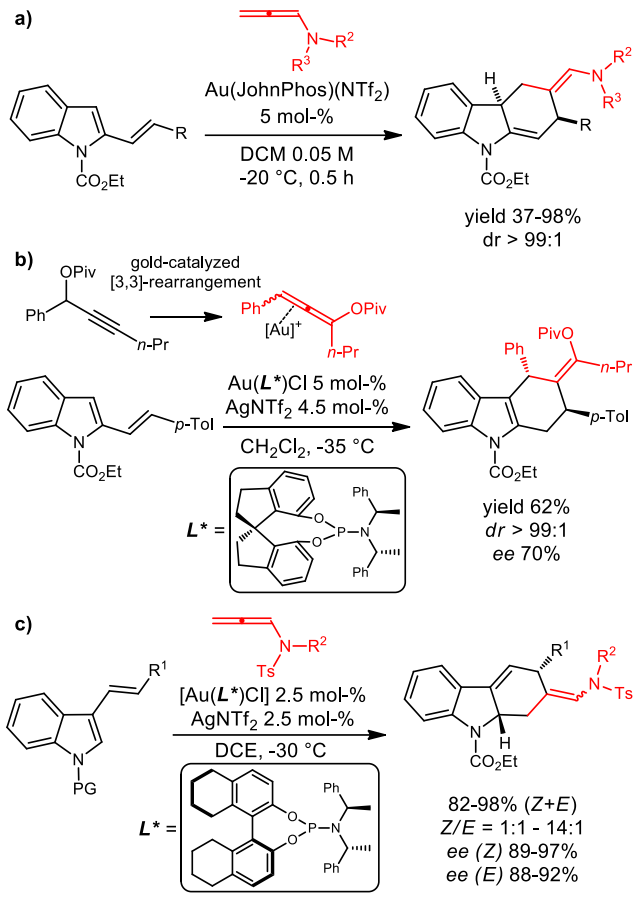
Carbazole and tetrahydrocarbazole rings are the key structural motif in a huge number of biological active molecules, including natural alkaloids and synthetic products.[1] For this reason, strategic syntheses of these indole derivatives are highly required, in particular when based on asymmetric methodologies. In this research field, 2- and 3-vinylindoles have become versatile four-carbon building blocks for the synthesis of complex tetrahydrocarbazole derivatives by means of [4+2] cycloaddition reactions with activated dienophiles.[2] Over the last years, the use of these heterocyclic dienes in Lewis acid[3] or organocatalyzed [4+2] cycloadditions[4] increased rapidly. However, application of these methodologies in enantioselective transformations is still limited and based mostly on organocatalytic methods. Thus, organocatalytic methodologies applied to enantioselective [4+2] cycloaddition reactions work either in the presence of hydrogen bond donor[5] or chiral phopsphoric acid[6] catalysts or through the generation of iminium ions[7] from enones and properly substituted secondary amines (Scheme 1).



Scheme 1. Enantioselective [4+2] cycloadditions of vinylindoles with classical dienophiles.

On the contrary, examples of asymmetric Lewis acid catalyzed [4+2] cycloadditions of 2- and 3-vinylindoles are quite rare and only recently some groups reported the development of chiral Lewis acid as active catalysts in these transformations (Scheme 1).[8]

Recently, it has been shown that gold activated allenes participate in a great number of intermolecular annulation reactions, including [4+2] processes.[9] Pionering work by Wang, Goeke[9m] and Mascareñas[9n] demonstrated that simple allenyl ethers and allenamides are efficiently activated towards the cycloadditions with dienes by gold(I) catalysts. In particular, reactions catalyzed by cationic gold triphenylphosphane or heterocyclic carbene complexes as well as by simple AuCl lead regioselectively to the corresponding cyclohexene derivatives. In both these works, the proposed reaction mechanism involves gold coordination at the terminal double bond of the allene followed by the formation of a gold-stabilized allylcation able to participate in the [4+2] cycloaddition reaction. Furthermore, Mascareñas and co-workers described the enantioselective version of these cycloadditions, performed with a new class of C–2 ligands featuring a triazole unit embedded to rigid cyclic framework.[9o] The reported reaction represents the first asymmetric intermolecular [4+2] cycloaddition promoted by a chiral carbophilic metal complex. According to the same heading, several papers dealing with [4+2] cycloadditions of 2- and 3-vinylindoles with allenes as dienophiles and occurring under gold-activation appeared in the literature (Scheme 2).[10]



Scheme 2. [4+2] cycloadditions of vinylindoles with allenes under gold-activation.

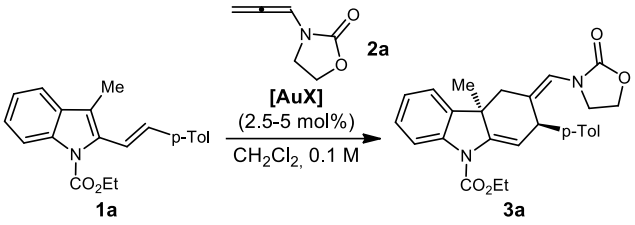
In particular, we published the first example of gold catalyzed reaction of 2- and 3-vinylindoles with allenamides[10a] (Scheme 2a) and allenyl esters (Scheme 2b).[10c] In this latter work we reported also some preliminary investigations on enantioselective synthesis of tetrahydrocarbazoles, reacting 2-vinylindoles and allenyl esters in the presence of a chiral gold(I) phosphoramidite catalyst. Therefore, under our best reaction conditions, we observed the formation of the desired product in good yield and with an encouraging *e.e.* of 70%. Moreover, related enantioselective reactions performed with 3-vinylindoles and allenamides were reported by Xia and Zhang (Scheme 2c).[10b] In particular, they studied the reactions of 3-vinylindoles with *N*-allenamides catalyzed by chiral H_8-BINOL-derived phosphoramidite gold(I) complex. However, both (*E*) and (*Z*)-isomers at the exocyclic double bond were isolated in variable ratios and each of them in good to excellent enantiomeric excesses.

Prompted by these results and taking into account the importance of asymmetric tetrahydrocarbazole synthesis, we decided to explore the reactivity of 3/2-substituted-2/3-vinylindoles with *N*-allenamides under chiral gold(I) catalysis for the synthesis of a new series of dearomatized indoles bearing a quaternary C4a/C9a stereocenter. Herein, we report the complete survey of the obtained results.

Results and Discussion

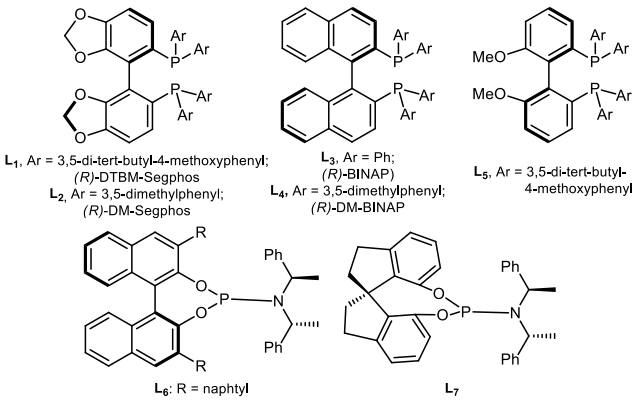
We started our investigations using 3-methyl-2-vinylindole **1a** and *N*-allenamide **2a** in a model reaction in order to evaluate the activity of various gold species. The obtained results are summarized in Table 1.

Table 1. Screening of reaction conditions for the synthesis of **3a**.[a]



Entry	Catalyst (mol%)	*T* [°C]	*t* [h]	Yield [%][b]	e.r.[c]
1	[Au(JohnPhos)(NTf$_2$)]	-20	1	75%	-
2	[**L$_1$**Au$_2$Cl$_2$]/AgNTf$_2$	-20	1	72%	93:7
3	[**L$_2$**Au$_2$Cl$_2$]/AgNTf$_2$	-20	1	54%	73:23
4	[**L$_3$**Au$_2$Cl$_2$]/AgNTf$_2$	-20	1	52%	63:37
5	[**L$_4$**Au$_2$Cl$_2$]/AgNTf$_2$	-20	1	75%	80:20
6	[**L$_5$**Au$_2$Cl$_2$]/AgNTf$_2$	-20	1	48%	88:12
7	[**L$_6$**AuCl]/AgNTf$_2$	-20	1	68%	46:54
8	[**L$_7$**AuCl]/AgNTf$_2$	-20	1	70%	67:33
9	[**L$_1$**Au$_2$(NTf$_2$)$_2$]	-20	1	81%	94:6
10[d]	[**L$_1$**Au$_2$(NTf$_2$)$_2$]	-75	3.5	18%	96:4
11	[**L$_1$**Au$_2$(NTf$_2$)$_2$]	0	1	61%	95:5
12[e]	**[L$_1$Au$_2$(NTf$_2$)$_2$]**	**-40**	**3**	**85%**	**96:4**[f]

[a] *Reaction conditions:* **1a** (0.2 mmol), *N*-allenammide **2a** (0.9 equiv.), gold(I) catalyst, [Au(JohnPhos)(NTf$_2$)] (5 mol%); **L$_1$-L$_5$** (2.5 mol%); **L$_6$-L$_7$** (5 mol%), AgNTf$_2$, when used, (5 mol%), in CH_2Cl_2 (0.1 M). [b] Isolated yield. [c] Determined by HPLC on pure isolated product. [d] Unreacted **1a** was recovered (>70%). [e] Performed with 1.2 equiv. of allenamide **2a**. [f] Increased to 99:1 after one single recrystallization. *JohnPhos* = (2-Biphenyl)di-*tert*-butylphosphine.



At first, in order to verify the feasibility of our proposal, we performed a preliminary reaction catalyzed by Au(JohnPhos)(NTf_2). By conducting the reaction in dichloromethane at -20 °C, we were pleased to observe the formation of **3a** as single diasteroisomer in 75% yield (Table 1, entry 1). The structure of **3a**, the *trans* relationship between the substituents on the polycyclic ring and the geometry of the exocyclic double bound were elucidated and demonstrated by mono- and bi-dimensional NMR analyses and by X-ray (figure 1).

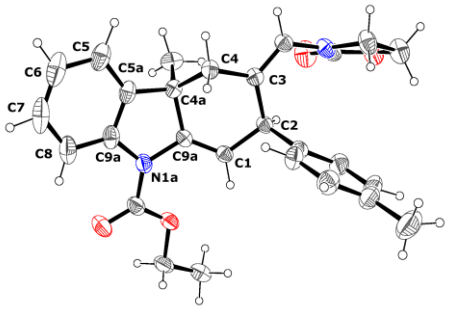


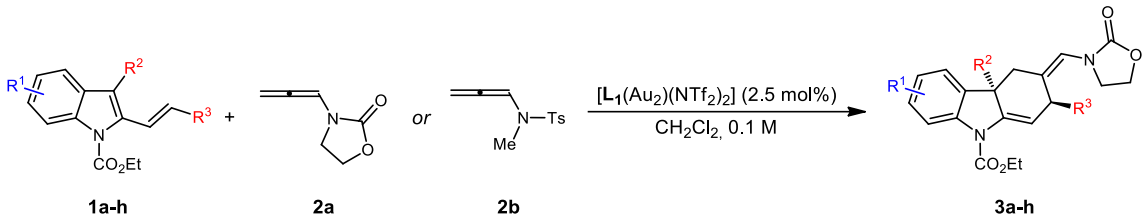
Figure 1. ORTEPIII plot of compound **3a** showing the numbering schemes for all non-hydrogen atoms of the tetrahydrocarbazole group. Ellipsoids drawn at 30% probability.

Then we moved to chiral gold(I) species.[9g],[11] In particular, we selected a set of bulky axially chiral biarylphosphine ligands (Table 1, $\mathbf{L_1}$-$\mathbf{L_5}$), characterized by electronic properties closely related to those of JohnPhos ligand. Next, the corresponding dinuclear gold(I) chloride complexes were prepared and used in the screening.[12] In the first enantioselective trial, the use of a chiral cationic catalyst generated in situ from (*R*)-DTBM-SegPhos($\mathbf{L_1}$)Au_2Cl_2 and $AgNTf_2$ afforded tetrahydrocarbazole **3a** in 72% yield and with a promising *e.r.* of 93:7 (Table 1, entry 2). Similarly, other biarylphosphine-based complexes were tested. (*R*)-DM-SegPhos($\mathbf{L_2}$)/gold(I) catalyst was less effective producing **3a** in both lower yield and *e.r.* (Table 1, entry 3). Likewise, BINAP derivatives $\mathbf{L_3}$ and $\mathbf{L_4}$ led to worse results with than (*R*)-DTBM-SegPhos ($\mathbf{L_1}$), affording **3a** in 52% and 75% yield, and with *e.r.* of 63:37 and 80:20, respectively (Table 1, entries 4 and 5). Lastly, cationic gold(I) complex arising from chiral biphenyl ligand $\mathbf{L_5}$ gave the desired product in quite good *e.r.* (88:12) but in modest 48% yield (Table 1, entry 6). For comparison we tested also the activity of chiral monodentate gold(I) phosphoramidites derived from C3,C'3 substituted-BINOL ($\mathbf{L_6}$) and from spirobiindane ($\mathbf{L_7}$) ligands. In both cases, despite the good yields, we observed a significant decrease of the *e.r.* to 46:54 using BINOL-derived $\mathbf{L_6}$ gold(I) (Table 1, entry 7) and to 67:53 with spirobiindanic $\mathbf{L_7}$ gold(I) species (Table 1, entry 8). Having selected (*R*)-DTBM-SegPhos ($\mathbf{L_1}$) as best chiral ligand, we decided to test the corresponding isolated cationic complex (*R*)-DTBM-SegPhos$Au_2(NTf_2)_2$ in order to avoid any possible interference arising from cationic silver and chloride anion on the reaction outcome. By using the isolated gold complex, the yield of **3a** was increased up to 81% retaining very similar *e.r.* (Table 1, entry 9). Then, we briefly investigated the role of the temperature on the reaction outcome. Performing the reaction at -75°C, we did not observe any substantial difference in terms of *e.r.*, but the cycloaddition proceeded slowly and, after 3.5 h, **3a** was isolated in only 18% yield beside a significant amount of starting vinylindole **1a** (Table 1, entry 10). Likewise, when we performed the reaction at 0°C we did not observe severe changes in the *e.r.*, however the yield dropped to 61% because of the formation of some unidentified side-products probably arising from the decomposition of *N*-allenamide **2a** (Table 1, entry 11). Finally, best results were obtained at -40 °C and in the presence of a slight excess of allene **2a** (Table 1, entry 12). Under these optimized reaction conditions, **3a** was prepared in 85% yield in 3 h and with an *e.r.* of 96:4, further increased to 99:1 after one single recrystallization in CH_2Cl_2/*n*-pentane at room temperature.

Based on these results, we next explored the scope of the dearomative [4+2] cycloadditions between 2-vinylindoles **1a-h** and allenes **2a-b** for the synthesis of tetrahydrocarbazoles **3** (Table 2).

By way of comparison, Table 2, entry 1 reports the results for the cycloaddition reaction of **1a** with **2a** under the optimized reaction conditions (Table 1, entry 10). The introduction of an ED group (OMe) on the aryl group at the vinyl moiety (2-vinylindole **1b**) led to **3b** in comparable yield and *e.r.* (Table 2, entry 2). On the contrary, the presence of a strong inductive EW substituent such as fluorine (2-vinylindole **1c**) negatively affected the yield. At -40 °C, the reaction was proceeding too slowly, therefore, it was necessary to increase the temperature up to 0 °C. After 18 h, **3c** was isolated in 40 % yield and with *e.r.* of 91:9 (Table 2, entry 3). This result could be probably due to the adverse influence of the conjugated EW substituent on the residual nucleophilicity of indole's C-3. A similar behavior was also observed when the EW group was located on the indole moiety. Thus, the reaction of 5-chloro-substituted 2-vinylindole **1d** required higher temperature and afforded **3d** in 61% yield and *e.r.* of 90:10 (Table 2, entry 4). Furthermore, the presence of an alkyl substituent at the vinyl moiety (vinylindole **1e**) was tolerated, even if both yield and enantioselectivity of the reaction were considerably decreased (Table 2, entry 5). We evaluated also the influence of the substituent on the C-3 of indole. Apart from methyl group, the reaction proceeded well also with the unsubstituted 2-vinylindole **1f**, and with the 3-ethyl derivative **1g** leading to carbazoles **3f** and **3g** in good yield and *e.r.* (table 2, entries 6 and 7). However, the reaction did not tolerate the presence of a C-3 phenyl ring (vinylindoles **1h**), and any product could be isolated (Table 2, entry 8).

Table 2. Scope of the reaction between 2-vinylindoles **1** and allenamides **2** under gold(I) catalysis.[a]



1a-h **2a** **2b** **3a-h**

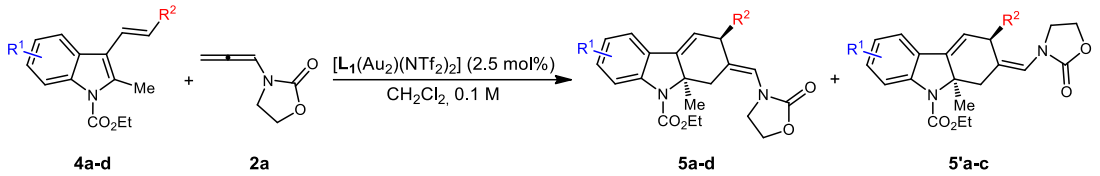
Entry	1	R^1	R^2	R^3	2	*T*, [°C]	*t*, [h]	Yield, [%][b]	*e.r.*[c]
1	**1a**	H	Me	4-Me-C_6H_4	**2a**	-40	3	**3a**, 85%	96:4[d]
2	**1b**	H	Me	4-OMe-C_6H_4	**2a**	-40	2	**3b**, 90%	97:3
3	**1c**	H	Me	4-F-C_6H_4	**2a**	0	18	**3c**, 40%	91:9
4	**1d**	5-Cl	Me	4-Me-C_6H_4	**2a**	0	3	**3d**, 63%	90:10
5	**1e**	H	Me	*n*-Pr	**2a**	0	4	**3e**, 48%	43:57
6	**1f**	H	H	4-Me-C_6H_4	**2a**	-40	18	**3f**, 81%	85:15
7	**1g**	H	Et	4-Me-C_6H_4	**2a**	-40	3	**3g**, 83%	85:15
8	**1h**	H	Ph	4-Me-C_6H_4	**2a**	0	18	–	–
9	**1a**	H	Me	4-Me-C_6H_4	**2b**[e]	0	5	**3h**, 51%	40:60

[a] *Reaction conditions:* **1** (0.2 mmol), *N*-allenammide **2a** (1.2 equiv.), chiral gold(I) catalyst (2.5 mol%), in CH_2Cl_2 (0.1 M). [b] Isolated yield. [c] Determined by HPLC on pure isolated product. [d] Increased to 99:1 after one single recrystallization. [e] **2b** (3 equiv.) added with syringe pump during 3 h, final concentration = 0.05 M.

Finally, we changed the nature of the *N*-allenamide, by testing the reactivity of *N*-tosyl derivative **2b**. The corresponding product **3h** was isolated in moderate yield (51%) and poor *e.r.* of 40:60 (Table 2, entry 9). In addition, this latter reaction was performed under carefully biased reaction conditions with the aim to minimize the dimerization of allenamide **2b.**[13]Considering the good results obtained with 3-substitued-2-vinylindoles **1**, we decided to briefly evaluate a possible extension of the scope to isomeric 2-methyl-3-vinylindoles **4** and allenamide **2a** (Table 3).

The reaction performed under the optimized conditions with 2-methyl-3-vinylindole **4a** and allenamide **2a** gave the corresponding isomeric dearomatized tetrahydrocarbazoles **5a** and **5'a** in 84% overall yield in 2.2/1 mixture (Table 3, entry 1). Isomeric **5a** and **5'a** were easily separated by flash chromatography and chiral HPLC analysis revealed that they were formed in high *e.r.*. The geometry of the exocyclic double bond was determined via mono and bidimensional NMR analysis (see supporting information). Similarly, 3-vinylindole **4b**, bearing an ED ethoxy group on the aryl at the vinyl moiety, afforded **5b** and **5'b** with high overall yield and *e.r.* (Table 3, entry 2). On the contrary, as observed for 3-methyl-2-vinylindoles **1**, the introduction of EW group at the same position of derivatives **4** affected the reactivity. For example, the reaction of 2-methyl-3-(4-fluorostyryl)indole **4c**, gave high yield of the corresponding tricyclic derivative **5c** (85%, *e.r.* 88:12) only when the temperature was raised to 0 °C (Table 3, entry 3). On the other hand, an ED group on indole moiety is well tolerated and **4d** afforded the corresponding products **5d** and **5'd** with high overall yield and *e.r.* for both carbazoles (Table 3, entry 4).

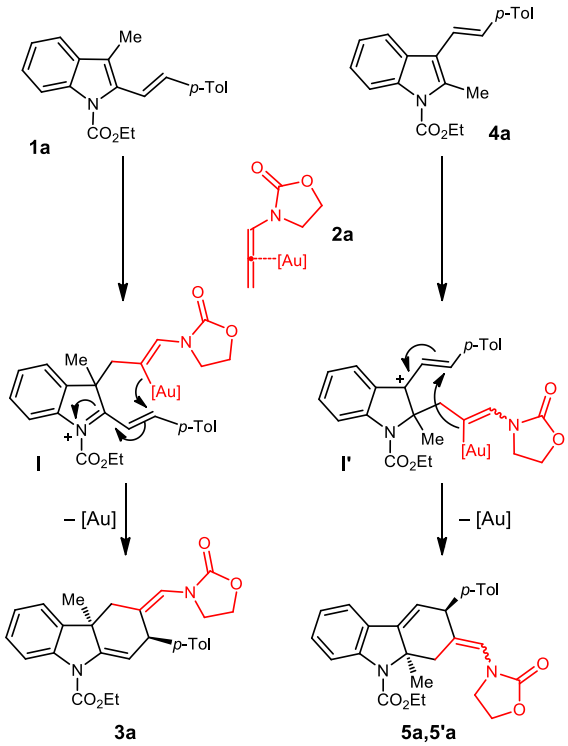
Table 3. Scope of the reaction between 3-vinylindoles **4** and allenamide **2a** under gold(I) catalysis.[a]



Entry	4	R^1	R^2	*T*, [°C]	*t*, [h]	Overall yield, [%][b]	5/5'	*e.r.*[c]
1	**4a**	H	4-Me-C_6H_4	-40	1.5	97%	2.2/1	**5a**: 92:8 **5'a**: 96:4
2	**4b**	H	4-OEt-C_6H_4	-40	1.5	80%	1/2.2	**5b**: 92:8 **5'b**: 99:1
3	**4c**	H	4-F-C_6H_4	0	3	85%	>20:1	**5c**: 88:12
4	**4d**	Me	4-Me-C_6H_4	-40	2	85%	1/1.6	**5d**: 92:8 **5'd**: 98:2

[a] *Reaction conditions:* **1** (0.2 mmol), *N*-allenammide **2a** (1.2 equiv.), chiral gold(I) catalyst (2.5 mol%), in CH_2Cl_2 (0.1 M). [b] Isolated yield. [c] Determined by HPLC on pure isolated product.

In accordance with our previous reports[10a,c] and with the results obtained by Zhang, Xia and coworkers[10b] in the cycloadditions of 3-unsubstituted-2-vinylindoles and 2-unsubstituted-3-vinylindoles, the mechanisms we proposed for the reaction of **1a** and **4a** with **2a** are very close as illustrated in Scheme 3.



Scheme 3. Proposed reaction mechanism for the [4+2] cycloadditions.

Thus, the reactions proceed via a stepwise mechanism initially with the formation of a new bond between C2 or C3 of indole and the external allene carbon atom affording the dearomatized cationic intermediates **I/I'**, respectively. The regiochemistry of the addition is dictated in both cases by the presence of an EW group at nitrogen and of the ED methyl group in position 2 or 3 on the indole nucleus.[10a-c,9e] The reactions then proceed with the formation of a second carbon-carbon bond restoring the catalyst and resulting in formal [4+2] cycloaddition products **3a** and **5a**/**5'a**. The stereochemistry around the external double bond in the final products is determined by steric factors. Thus, when the steric hindrance around the double bond in the first intermediate is small the reactions resulted in the isolation of both (*Z*) and (*E*) isomers.[10b]

Theoretically, the use of these 2,3-disubstituted indoles as dienes would have made the [4+2] cycloaddition more challenging because of plausible regioselection issues in the formation of the proper intermediates. In fact, since these reactions proceed via a stepwise mechanism,[10] the formation of the key reaction intermediates **I/I'** depends on the selective nucleophilic attack of indole C3 or C2 on allenamide and is essential for the further cyclization step leading to the final reaction products. However, products arising from a complementary regiochemical path has been never observed or detected.

Conclusion

In conclusion, we reported an asymmetric gold(I) catalyzed [4+2] cycloaddition of 3-substituted 2-vinylindoles and 2-methyl-3-vinylindoles with *N*-allenamides. In most cases, the reactions proceeded

with satisfactory yields and with good to excellent *e.r.* Thus, we introduced the first dearomative [4+2] cycloaddition of 2,3-disubstituted-vinylindoles with simple π-systems as dienophiles for the easy construction of chiral carbazole derivatives bearing a quaternary stereogenic center at C4a (compounds **3**) or at C9a (compounds **5**, **5'**). This study well complements previous studies on the enantioselective dearomative [4+2] cycloaddition of 3-substituted-2-vinylindoles with classical activated dienophiles[13] and related studies in the field of gold-mediated [4+2] cycloaddition reactions of vinylindoles with allenes.[10]

Experimental Section

Typical procedure for the synthesis of tetrahydrocarbazoles 3

To a solution of [(*R*)-DTBM-SegPhos$Au_2(NTf_2)_2$] (0.005 mmol, 2.5 mol %) in CH_2Cl_2 (1.0 ml), 3-substitued-2-vinylindole **1a-h** (0.2 mmol, 1.0 equiv.) was added and the mixture was cooled to -40 or 0 °C. Then, a solution of *N*-allenamide **2a-b** (0.22 mmol, 1.2 equiv.) in CH_2Cl_2 (1.0 ml, final concentration ca. 0.1 M) was added dropwise and the reaction was stirred at the same temperature until disappearance of the starting materials (checked by TLC, see Table 2). The reaction was quenched with PPh_3 (0.03 mmol, 15 mol %) and the solvent was removed under vacuum. Purification by column chromatography yielded the corresponding tetrahydrocarbazoles **3a-h**.

Supporting Information Available

Detailed descriptions of experimental procedures and the spectroscopic data of the products as well as the crystal structures are presented in the Supporting Information. CCDC 1536255 (**3a**) 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.

Acknowledgements

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