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Minireview

Gold Catalysts

Vinyl-/Furoindoles and Gold Catalysis: New Achievements and Future Perspectives for the Synthesis of Complex Indole Derivatives

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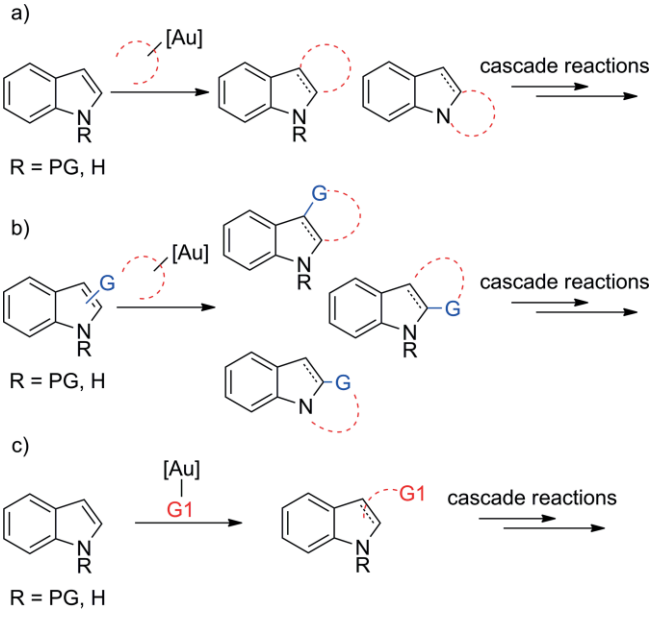
Abstract: The reactivity of vinyl-/furoindole derivatives with gold-activated π-systems is the subject of extensive investigation. In the presence of these electrophilic partners, the realized transformations allow for the construction of different and fascinating architectures via cycloaddition and cyclization reactions often included in cascade processes. The reactions realized involving in these processes an external substituent at the indole moiety are the subject of the present minireview.

1. Introduction

Indoles met gold catalysis in the early 2000s when the first reports on the inter and intramolecular gold(I) and gold(III) catalyzed functionalization of indoles with alkynes, allenes and alkenes appeared in the literature.[1] Thus, the activation of these π-systems by gold catalysts furnishes the "ideal" electrophilic partners for the electron-rich indole heterocycle. In the following years, this apparently simple reaction scheme has been extended to more complex indoles and challenging unsaturated systems allowing for the synthesis of polycyclic or highly substituted indole derivatives. The reported methodologies involve either cyclization and cycloaddition reactions or cascade and multicomponent reactions.[2] In Scheme 1, we exemplify the general reaction pathways involving indoles and gold-activated π-systems. Therefore, the cyclization processes can involve both C2–C3 double bond and N–C2 bond of the starting indoles, Scheme 1a. Moreover, an external substituent can take part in these reactions allowing for the construction of different motifs, Scheme 1b. It is worth to note that in both cases the primary cyclization compounds can evolve toward the formation of rearrangement products expanding the scope of these transformations via cascade processes. These latter can be also realized thru sequences involving simple functionalization followed by rearrangement reactions, Scheme 1c.

Starting from 2013, we have been actively involved in gold catalyzed transformations of the type reported in Scheme 1b, which are the topic of this minireview.

For example, at the beginning of our investigation, we described the cycloaddition reactions of vinylindoles **1** with Lewis acids activated electron-poor alkenes, Scheme 2.[3] The reaction occurs in the presence of $BF_3(OEt_2)$ via a [4+2] cycloaddition



Scheme 1. Gold-catalyzed synthesis of polycyclic and complex indoles.

followed by 1,3[H]-shift giving rise to the corresponding tetrahydrocarbazoles **3/3'** in good diastereoisomeric excesses. Then, for the same reactions, we compared the catalytic activity of gold salts and complexes to traditional Lewis acids.[3c] The best performing catalysts were gold(III) chloride and $Au(PPh_3)Cl$/AgOTf giving rise to results in line with those obtained with the best performing Lewis acid catalysts. Moreover, although gold catalysts can act both as σ-[4] and π-philic activators,[5] in all tested reactions the gold catalysts acted as an effective σ-philic Lewis acid able to activate the enone cycloaddition partner.

Beside gold, also other coinage metals such as copper and silver are able to promote the cycloaddition reactions of vinylindoles with classical dienophiles (copper)[6] or unactivated π-systems (silver).[7] Later on, we moved our attention to the

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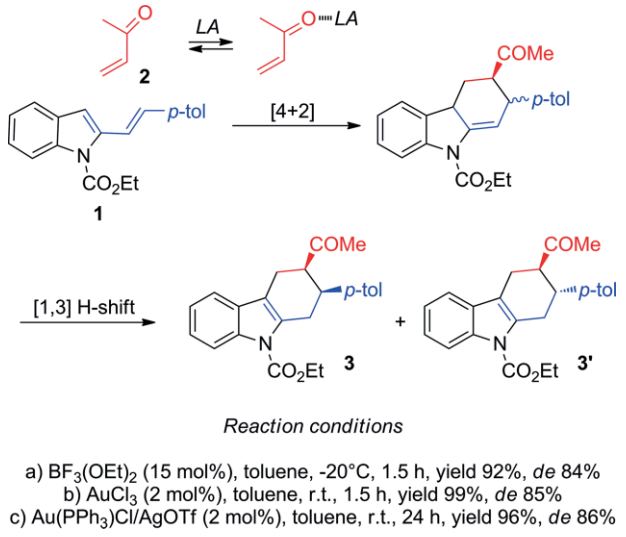


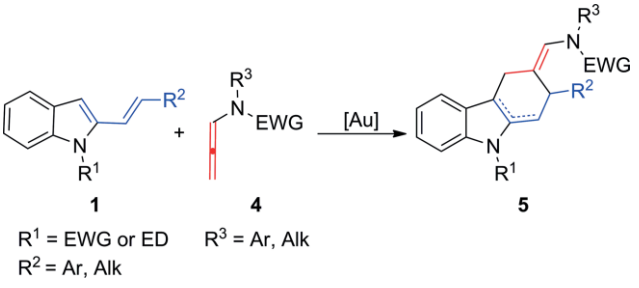
Scheme 2. Lewis acid and gold catalyzed cycloaddition reactions of 2-vinylindoles 1 with electron-poor alkenes **2**.

[4+2] cycloaddition reactions of vinylindoles with gold activated π-systems. In particular, we exploited the reactivity of 2-vinyl and 3-vinylindoles (section 2) as well as 4*H*-furo[3,2-*b*]indoles (section 3) with different unsaturated systems for the synthesis of polycyclic indoles as well as of complex indole derivatives.

In this minireview, we report the results obtained by us and by other research groups, active in the same or related research fields, on gold catalyzed transformations of the type reported in Scheme 1b. A final section (section 4) reports a critical survey of the obtained results and the possible and desirable expansions of this chemistry.

2. Reactivity of 2-Vinyl and 3-Vinylindoles with Gold-Activated Allenes

In our first investigation, we used 2-vinylindoles **1** as 4π-components in [4+2] cycloadditions with gold-activated allenes **4**[8] for the synthesis of 3-amidomethyliden-tetrahydrocarbazoles **5**, Scheme 3.[9]



Scheme 3. [4+2] cycloaddition between 2-vinylindoles **1** and allenes **4**.

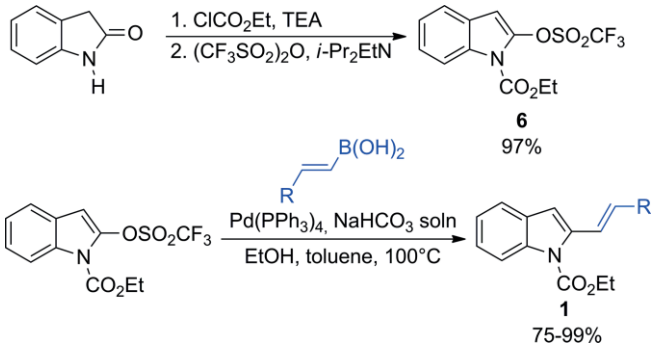
Valentina Pirovano was born in Bergamo (Italy) in 1986. In 2010, after a six-month stay in the research group of Prof. Lutz Ackerman (University of Göttingen), she obtained her master's degree in Pharmaceutical Chemistry and Technology at the University of Milan (Italy). From 2011 to 2014 she pursued a co-tutored Ph.D. under the supervision of Prof. Elisabetta Rossi (University of Milan) and Dr. Rubén Vicente (University of Oviedo, Spain). Since 2014, she has been working as a postdoctoral researcher in the group of Prof. Elisabetta Rossi, focusing her studies on transition-metal catalysis applied to the synthesis and the functionalization of heterocyclic moieties.

Giorgio Abbiati received the B.Sc. degree in Pharmaceutical Chemistry and Technology in 1997 and the Ph.D. in Pharmaceutical Sciences in 2000 from the University of Milan. In 2005, he was appointed Assistant Professor (Researcher) at the Department of Medicinal Chemistry of the University of Milan and became Associate Professor in 2015. He is lecturer in Organic Chemistry and Environmental Chemistry at the University of Milan. His research is focused on the study of novel synthetic methodologies for the preparation and the functionalization of heterocyclic compounds. From a methodological point of view, main interest are devoted to homogeneous metal catalysis (in particular Ag, but also Cu, Au and Pd), domino and multicomponent approaches and MAOS (Microwave-Assisted Organic Synthesis). The main topic is the study of synthetic potential of arylacetylenes bearing a proximate reactive group for the preparation of oxygen- and nitrogen-containing heterocycles, also in their polycyclic forms.

Elisa Brambilla was born in Monza (Italy) in 1993. In 2017, she obtained her master's degree in Pharmaceutical Chemistry and Technology at the University of Milan (Italy). Since 2017, she has been pursuing a Ph.D. under the supervision of Prof. Elisabetta Rossi (University of Milan). Since 2019 she has been working as a PhD researcher in the laboratories of professor A. Stephen K. Hashmi (Heidelberg University), focusing her studies on functionalization of heterocyclic compound to synthesize complex derivatives under metal catalysis.

Elisabetta Rossi received her master's degree in Pharmaceutical Chemistry and Technology in 1981 from the University of Milan. In 1984, she obtained a specialization qualification in Analytical and Chemical Methodologies for Fine Chemicals at the Politecnico of Milan. She is currently full professor at the Department of Pharmaceutical Sciences at the University of Milan. Her research activity is focused on the study of new synthetic methodologies for the synthesis and functionalization of heterocyclic compounds through domino and cascade approaches, intramolecular cyclization, and cycloaddition reactions catalyzed by Lewis acids or transition metals (In, B, Sc, Ti, Pd, Au, and Ag).

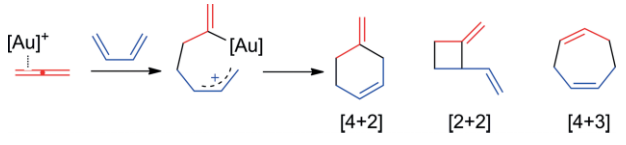
We became involved in the chemistry of 2-vinylindoles since 2006 when we published the synthesis of a new stable indolyl triflate **6**, Scheme 4.[10]



Scheme 4. Stereoselective synthesis of 2-vinylindoles **1**.

Compound **6** can participate in palladium catalyzed Suzuki–Miyaura reactions with vinylboronic acids for the stereospecific synthesis of *E*-2-vinylindoles **1** in good to excellent yields.

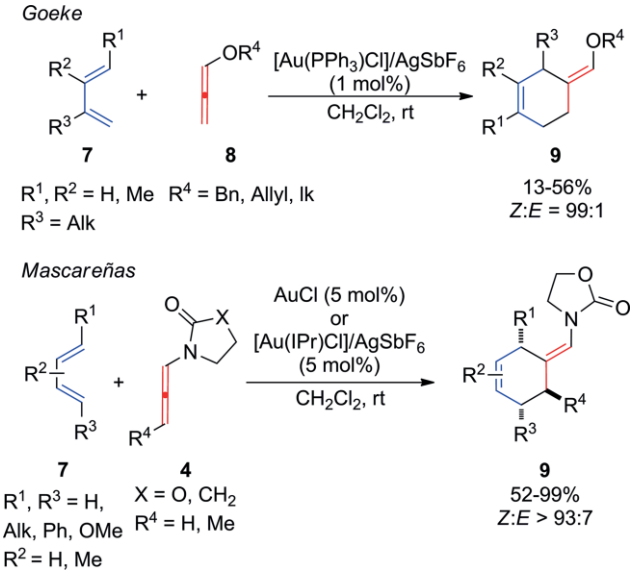
When π-systems and in particular dienes are involved as nucleophiles in the reactions with gold-activated allenes, the formation of a bond normally occurs at the external allene carbon and may be coupled with the creation of a second C–C bond in a concerted or stepwise fashion resulting in formal [4+2], [2+2] and [4+3][11] cycloaddition products, Scheme 5.[12]



Scheme 5. Gold(I) activated allenes and dienes: plausible cycloaddition mode.

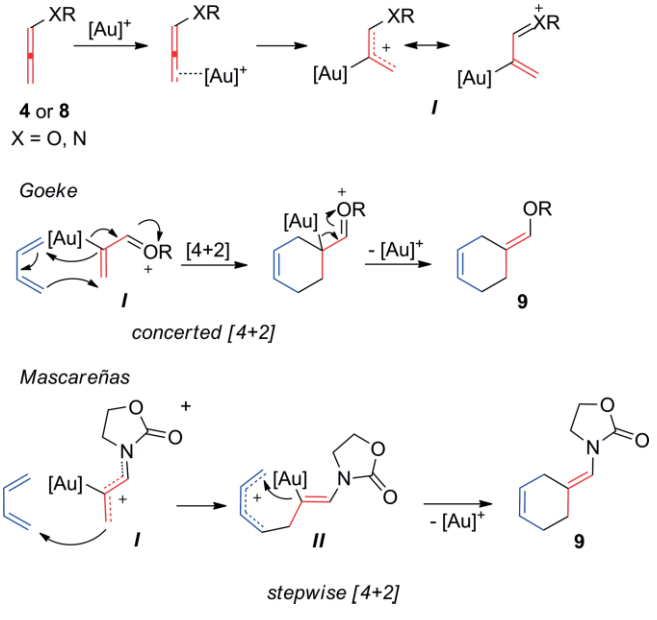
Thus, allenes can participate as C2 or C3 synthons in cycloaddition reactions. Initially, this kind of reactivity has been widely studied in intramolecular processes.[13] Thereafter, in 2011, Goeke[14] and Mascareñas[15] independently described the first examples of the intermolecular cycloadditions between acyclic dienes **7** and, respectively, alkyl allenyl ethers **8** or allenamides (in this review the term "allenamide" refers to N–C=O substituted allenes) **4** for the synthesis of cyclohexene derivatives **9**, Scheme 6.

Alkyl allenyl ethers **8** and allenamides **4** were efficiently activated towards the cycloaddition with acyclic dienes by cationic gold(I) triphenylphosphane catalyst, [Au(Ph$_3$P)(SbF$_6$)], or by simple AuCl leading to the corresponding cyclohexene derivatives **9**. The reaction outcomes strictly depend on the nature of the substrates employed. Reactions performed with allenyl ethers seem to be more challenging and the corresponding cyclohexenes were formed only in poor yields employing simple acyclic dienes and in moderate yields using more reactive acyclic dienes such as *homo*-myrcene. However, excellent results in terms of regio- and diastereoselection were obtained. The scarce chemical yields could be related to the inherent instability of allenyl ethers that decompose when prolonged reaction times are required. This statement finds a confirmation looking at the results obtained by the same authors in the reaction with cyclic



Scheme 6. Gold-catalyzed [4+2] cycloaddition between acyclic dienes **7** and allenes **8** or **4**.

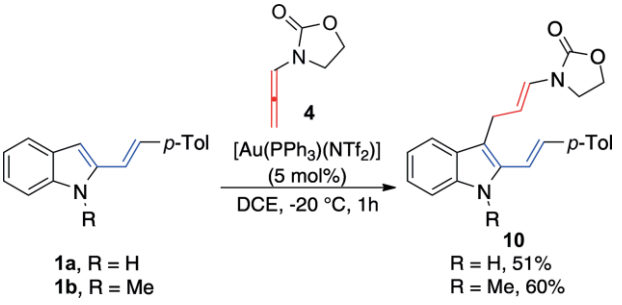
dienes (cyclopentadienes and alkylcyclopentadienes). These more reactive substrates yield the corresponding cyclohexenes in good to excellent yields even if regio- and diastereoselections are lower. Meanwhile, using allenamides and acyclic dienes excellent results in term of yield, regio- and diastereoselectivity were achieved by Mascareñas, which reported also the only example on the use of a chiral disubstituted allenamide bearing a methyl group at the distal position. In both reactions, the proposed mechanism involves gold coordination at the external double bond of the allene moiety followed by the formation of the gold-allyl cation ***I***, stabilized by the presence of the oxygen or the nitrogen atom, respectively, Scheme 7.



Scheme 7. Concerted or stepwise [4+2] cycloadditions involving stabilized gold-allyl cation ***I***.

Intermediate ***I*** can then react with the diene in a concerted or stepwise fashion, giving rise to final cyclohexene derivatives after deauration. Theoretical calculation made by Goeke demonstrated the effectiveness of a concerted [4+2] mechanism for the reaction of allenyl ethers with both cyclic and linear dienes. Moreover, they demonstrated that the preferred *Z* geometry at the exocyclic double bond was related to the stability of the exo vs. endo-transition state of the reaction. On the other hands, Mascareñas suggested a stepwise [4+2] mechanism in which intermediate ***I*** reacts with the nucleophilic diene affording a new nitrogen stabilized cationic intermediate ***II***. Final intramolecular enamide attack over the less encumbered carbon atom in intermediate ***II*** furnishes the final [4+2] cycloadduct after deauration. The control experiments realized performing the reaction between allenamides and dienes in the presence of methanol supported the consistency of the proposed stepwise mechanism. Moreover, the proposed reaction mechanism accounts for the isolation, in low yields, beside the [4+2] products, of the [2+2] cycloadducts arising from intermediate ***II*** by intramolecular nucleophilic attack of enamide over the internal carbon atom of the allyl moiety. The amount of [2+2] products strictly depends on the nature of the catalyst used even if the authors did not evaluate the conditions for the exclusive formation of the cyclobutane derivatives. For example, IPrAuCl/$AgSbF_6$ triggers the reaction toward the formation of [4+2] and [2+2] cycloaddition products in 41 and 16 % yield, respectively.

Starting our studies for the reaction of 2-vinylindoles with allenamides,[9] Scheme 8, we found that the use of vinylindoles **1a–b** bearing methyl or hydrogen at N1 gave rise to hydroarylation products **10** in moderate yields when using the cationic gold catalyst [Au(PPh_3)(NTf_2)].

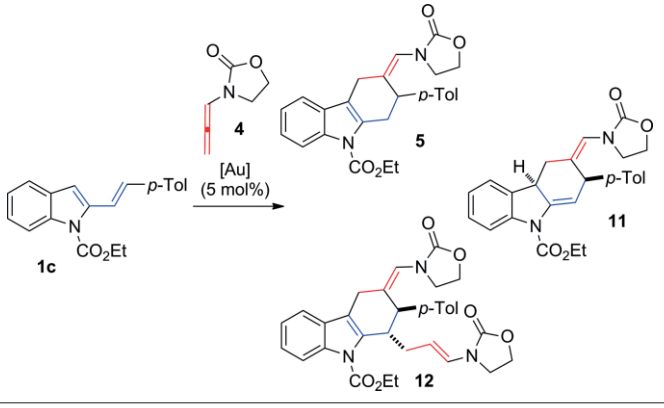


Scheme 8. Gold-catalyzed reaction between NH/N–Me 2-vinylindoles **1a–b** and allenamide **4**.

Indeed, when we employed vinylindole **1c**, Table 1, bearing a carbamate at nitrogen, under the previous reaction conditions, the 3-amidomethyliden-tetrahydrocarbazole **5** arising from a [4+2] cycloaddition/[1,3]hydrogen shift process was isolated along with a non-aromatized carbazole **11** arising from a simple [4+2] cycloaddition process not followed by hydrogen shift and an unexpected tetrahydrocarbazole **12**. It is worth to note that all tetrahydrocarbazoles were obtained as single chemo-, regio- and diastereoisomers as demonstrated by single-crystal X-ray analysis. Moreover, compound **12** arises from a three components process involving one molecule of vinylindole and two molecules of the allene, a process that is less common in gold catalysis and not reported before in cycloadditions with allenamides. Thus, a more detailed study was carried out in order to identify the best reaction conditions for the selective synthesis of **5**, **11** and **12**, Table 1.

We performed a first screening in the presence of 0.9 equivalents of allenamide with various gold catalysts and those giving

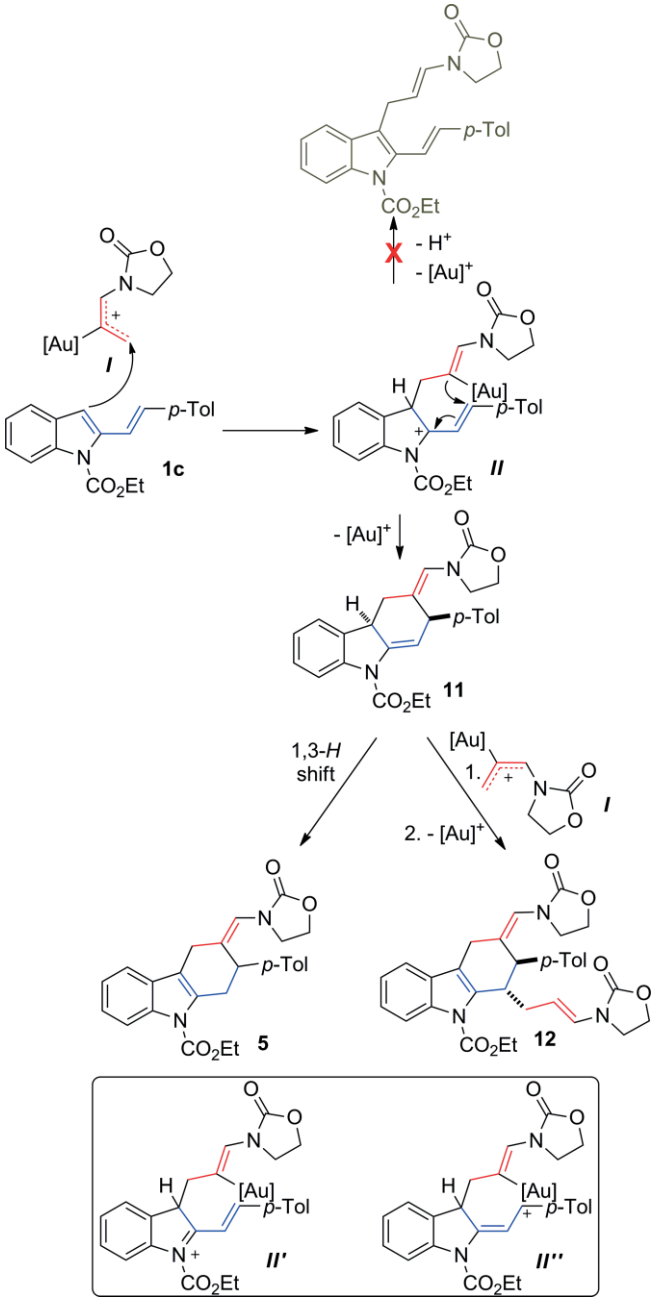
Table 1. Screening of conditions for the selective synthesis of **5**, **11** and **12**.



Entry[a]	**4**, n *equiv.*	[Au] (5 mol-%)	Solvent, [M]	**5** [%]	**11** [%]	**12** [%]
1	0.9	[Au(IPr)(NTf_2)]	DCE, 0.1 M	5	75	–
2	0.9	[Au(JohnPhos)(NTf_2)]	DCE, 0.1 M	–	81	8
3	0.9	[Au(PPh_3)(NTf_2)]	DCE, 0.1 M	54	–	9
4	0.9	[Au($(ArO)_3P$)(NTf_2)]	DCE, 0.1 M	65	18	–
5	0.9	[Au(JohnPhos)(NTf_2)]	CH_2Cl_2, 0.05 M	–	80	–
6	2.5	[Au(JohnPhos)(NTf_2)]	CH_2Cl_2, 0.05 M	–	–	95
7[b]	0.9	$AuCl_3$	CH_2Cl_2, 0.05 M	83	–	–

[a] Isolated yields. [b] Performed at –50 °C. IPr = Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]; JohnPhos = (2-Biphenyl)di-*tert*-butylphosphine; Ar = 2,4-di-*tert*-butylphenyl.

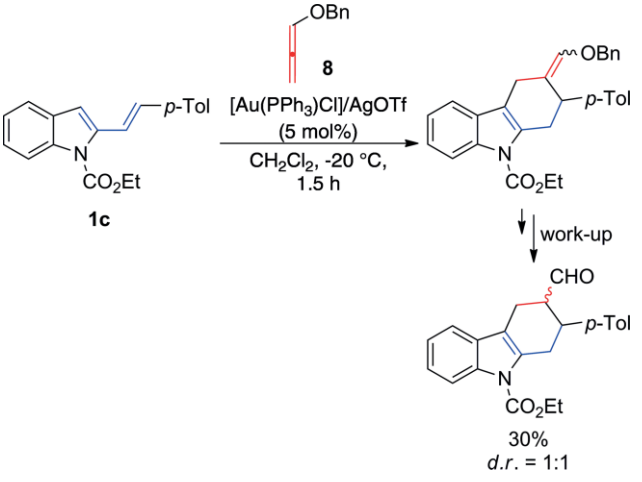
rise to superior selectivity are listed in Table 1 from entry 1 to entry 4 in roughly increasing order of electrophilicity.[16] They are all preformed cationic species with triflimide as counterion and as ligands a heterocyclic carbene, two phosphines (JohnPhos and PPh_3) and a more electrophilic triarylphosphite. Next, further experiments were conducted for the synthesis of **11** and in particular, using [Au(JohnPhos)(NTf_2)] a dilution of the reaction mixture resulted in the isolation of **11** in 80 % yield as single reaction product (entry 5). The selective synthesis of multicomponent product **12** in 95 % yield was achieved under the same reaction conditions using of an excess of allene (entry 6). Moreover, we found that the use of simple electrophilic Au(III) chloride favors the aromatization process affording **5** as single product in 83 % yield (entry 7). Having the optimized reaction conditions for the selective synthesis of **5**, **11** and **12**, we next evaluated the scope of these cycloadditions. Wide reaction scope was observed and modifications at the vinyl moiety and at the indole core as well as at the allenamide function are well tolerated. For the reactions performed with *N*-tosylallenamides a loss of stereoselectivity at the exocyclic double bond is somewhat observed. Finally, we found that the reaction works well also with allenamides and 2-vinylbenzofuran or 3-stirylindole as dienophiles. Due to the high polar character of the reacting substrates and intermediates, we assumed that the reaction proceeds via a fast, stepwise path, Scheme 9.



Scheme 9. Proposed mechanism for the reaction between **4** and **1c**.

A plausible mechanistic rationale[17] comprises the formation of the gold-allyl cation ***I*** followed by the nucleophilic attack of the indole through position C-3 affording intermediate ***II***. Then cyclization occurs, in a process, which is faster than protodemetallation. This cyclization leads to carbazole **11**, which in turn evolves to the aromatized indole **5** or undergoes a hydroarylation reaction with a second molecule of gold-activated allene ***I*** to afford **12** after aromatization and protodemetallation. The driving force to the exclusive formation of the cycloaddition product over the hydroarylation reaction could be related to the presence of the EWD group at N1 that can lower the nucleophilic character of the indole nitrogen, and thus the relative contribution of cationic species ***II'*** and ***II''*** with respect to ***II***. The enhanced electrophilic character of the outer carbon atom of the vinyl system favors the cyclization process.

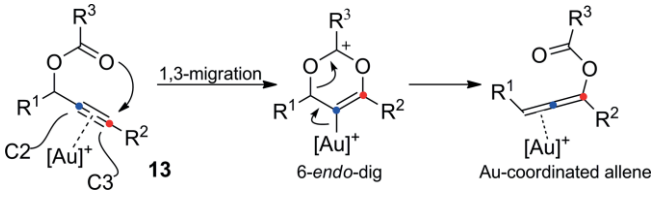
Apart from allenamides, we were interested in expanding the reaction to other allenes.[18] However, the use of other allenyl derivatives, such as allenyl ethers **8**, led to unsatisfactory results in terms of E/Z selectivity and yield, Scheme 10.



Scheme 10. Gold-catalyzed reaction between **1c** and allenyl ether **8**.

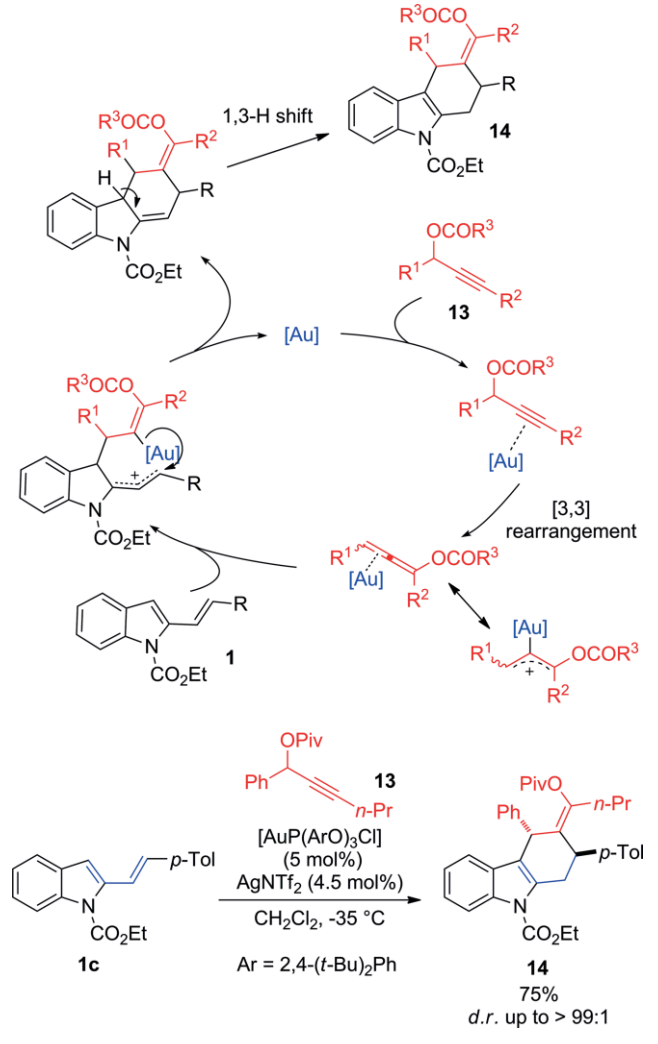
Furthermore, purification of the reaction crude led to isolation of the corresponding aldehydes, arising from hydrolysis of the vinyl ether group, as a 1:1 mixture of diastereoisomers. To address these difficulties, we envisioned the possibility of using allenyl esters as allenyl ether surrogates, Scheme 11.

Importantly, allenyl esters can be prepared from propargyl esters **13** via 3,3-rearrangement in the presence of cationic gold(I) catalysts and the use of highly electrophilic cationic gold



Scheme 11. Generation of allenyl esters by gold-catalyzed [3,3]-propargylic rearrangement of propargyl esters **13**.

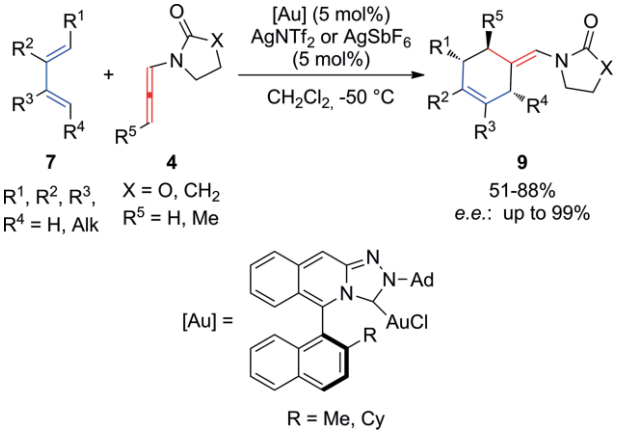
catalyst enables not only the generation of the allenyl ester but also its subsequent activation for further transformations via cascade reactions.[19] So for our purposes both the [3,3]-propargylic rearrangement of **13** and [4+2] cycloaddition could be catalyzed by the same gold species giving access to functionalized products via a cascade reaction. As expected the catalyst of choice was the electrophilic cationic gold(I) tris(2,4-di-*tert*-butylphenyl)phosphite and optimization of the reaction condition led to the isolation of the desired carbonyloxymethylidentetrahydrocarbazole **14** in 75 % yield, Scheme 12.



Scheme 12. Gold-catalyzed cascade [3,3]-propargylic rearrangement/[4+2]-cycloaddition of 2-vinylindoles **1** and propargyl esters **13**.

According to the screening, we then studied the scope of the present transformation. Modifications at the indole nucleus as well as at the propargyl alcohol are allowed and the corresponding tetrahydrocarbazoles **14** were obtained in good yields. In addition, terminal alkyne could participate in these reactions even if the product was obtained in modest 35 % yield.

Finally, we focused our attention on the enantioselective version of these and related reactions. Achieving enantioselectivity by means of gold catalysis is a challenging goal because both the linear two-coordination mode of gold(I) complexes and the out-sphere π-activation mode, place chiral ligands far apart from the reacting center, thus limiting the capacity to transfer the chiral information to the substrates.[20] A number of strategies to overcome this problem have been developed, most of them based on the use of new bulky chiral gold complexes with different steric and electronic properties. In a work which represents the evolution of that shown in Scheme 6, Mascareñas and co-workers reported the first example of a highly enantioselective intermolecular [4+2] cycloaddition between allenamides **4** and acyclic dienes **7** catalyzed by a chiral cationic gold(I) complex.[21] The work also represents the first asymmetric intermolecular [4+2] cycloaddition promoted by a chiral carbophilic metal complex, Scheme 13.



Scheme 13. Enantioselective [4+2]-cycloaddition between **7** and **4**.

The reaction provided a variety of cyclohexenone derivatives **9** with *ee* up to 99 % using as ligand for the gold(I) a new chiral carbene featuring a triazole-based NHC fused to a rigid C-2 asymmetric framework. The design of this new catalyst started with the observation that achiral NHC were able to catalyze the reaction and that chiral triazole-based NHCs have been successfully used in asymmetric organocatalysis.[22] The evolution from known ligands to the new chiral ones is reported in Figure 1.

Bode's triazolylidene chiral ligand **A**[23] promoted the formation of cyclohexenones in 91 % yield and 16 % ee. On the other hand, the research group of Lassaletta synthesized, inter alias, a new class of [1,2,4]triazolo[4,3-a]pyridin-3-ylidene NHC ligands **B**.[24] On these basis Mascareñas and co-workers designed and synthesized a new type of gold complexes **C**. The effectiveness of this catalyst can be related to the proximity of the cyclohexyl substituent R^1 to the gold center and to the modulatory effect exerted by the bulky adamantly group R^2.

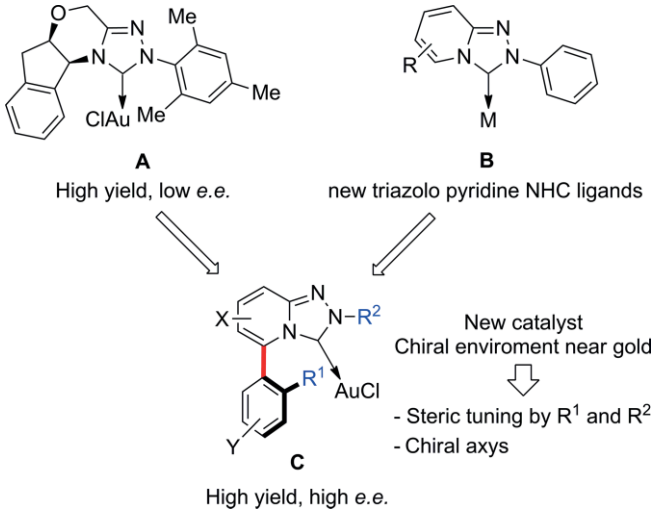
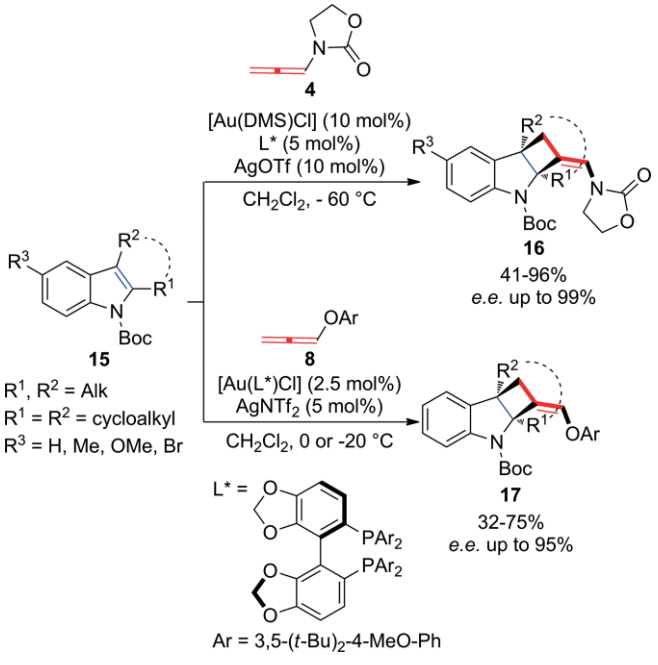


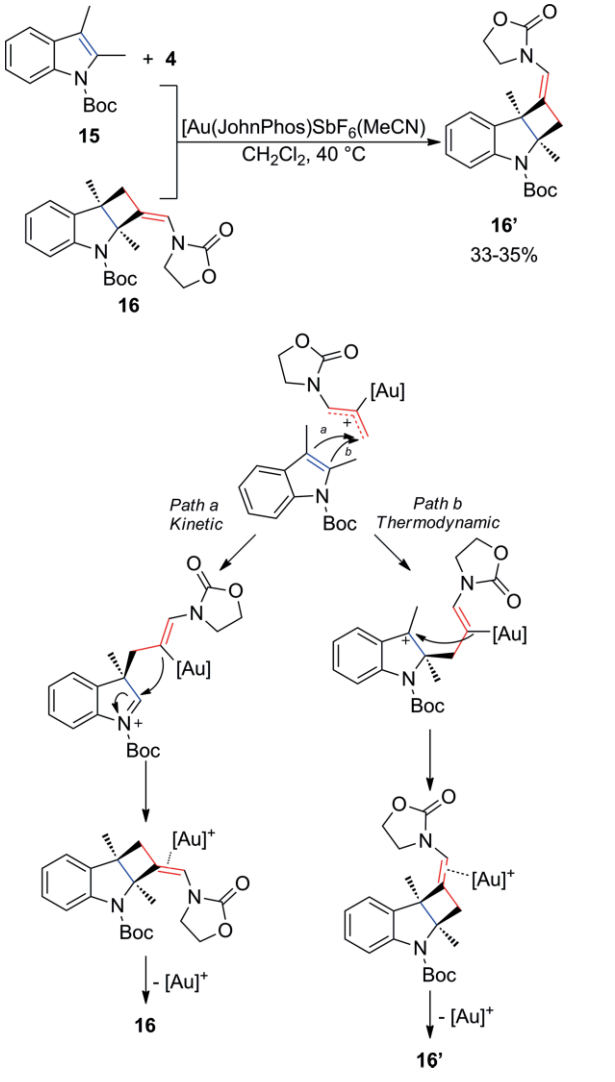
Figure 1. Design of chiral triazole-based NHCs.

Moreover, Bandini developed a dearomative formal [2+2]-cycloaddition reactions involving indoles **15** and allenamides **4** and giving rise to 2,3-cyclobutane-fused indolines **16**. DTBM-Segphos, a dinuclear chiral gold catalyst, was used to achieve the desired compounds with ee up to 99 %, Scheme 14.[25]



Scheme 14. Dearomative [2+2] cycloadditions of indoles **15** and allenes **4** and **8**.

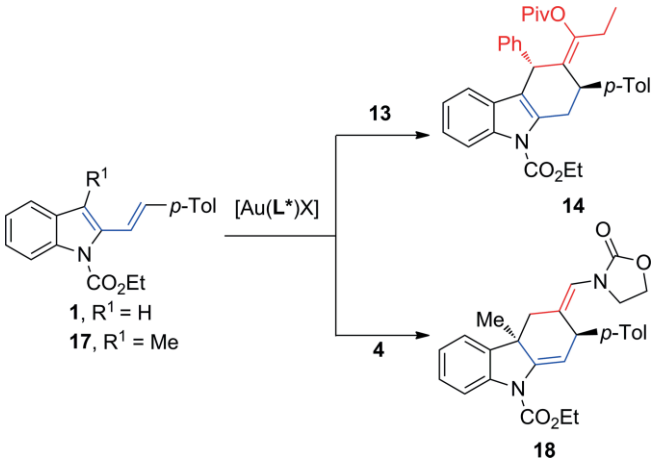
The screening for the best chiral ligand was performed using commercially available mono and dinuclear ligands. The gold(I) complex showing the best performances in the primary screening was then used for the fine tuning of the counterion for the cationic gold(I) complex and of the reaction conditions. Bandini and co-workers expanded the scope of these dearomative [2+2] cycloadditions to aryloxyallenes **8** (Scheme 14) for the synthesis of 2,3cyclobutane-fused indolines **17**. Moreover, they combined the experimental work with a computational study demonstrating that the reaction proceeds via a two-step process, Scheme 15.[26]



Scheme 15. Formation of regioisomeric **16′** and proposed two steps polar non-concerted mechanism.

In particular, they noticed that when the reaction was conducted at 40 °C regioisomeric [2+2] cycloadducts **16′** was the main reaction product. Moreover, **16′** was formed also by treating **16** at 40 °C with the gold(I) complex suggesting the existence of a kinetic (**16**) and a thermodynamic (**16′**) compound. Thus, a detailed computational study demonstrated the existence of two reaction pathways both involving a two steps polar non-concerted mechanism. Both reaction paths start from a common initial complex in which the indole ring and the metal allyl cation planes face each other. Then two separate reaction paths provide the two regioisomers detected experimentally. Regioisomer **16** obtained under kinetic control and **16′** under thermodynamic conditions. It is worth to note that the second step in both reactions involves the formation of the cyclobutene ring through the heterolytic rupture of the sigma [Au]–C bond and not the electrons of the exocyclic double bond. This observation accounts for the retention of the Z stereochemistry for the C=C double bond.

In this context, we studied the enantioselective version of our cascade reactions between 2-vinylindoles **1** and propargyl esters[11] **13** and between a new class of 2-vinylindoles **17**, bearing a methyl group at C-3 position, with allenamides **4**[27] for the synthesis of enantioenriched tetrahydrocarbazoles **14** and dearomatized indole derivatives **18**, Scheme 16.



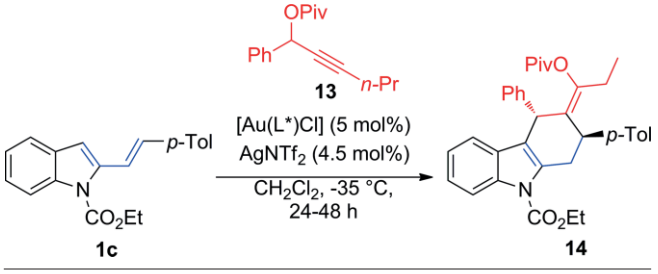
Scheme 16. Gold-catalyzed enantioselective synthesis of **14** and **18**.

In the first screening, Table 2, we tested several chiral electron-rich phosphoramidites ligands pertaining to the class of BINOL and spirobiindane derivatives (L_1–L_4) and a chiral phosphite ligand (L_5). All these ligands deliver high electrophilic cationic gold(I) complexes that would be able to trigger both the [3,3] rearrangement of the propargyl alcohol to allenyl ester and the formation of the corresponding gold-activated species.

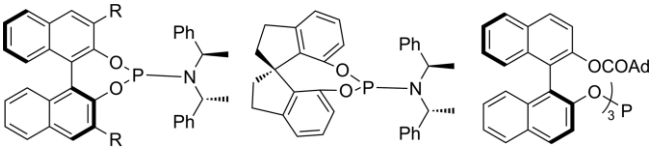
In general, what we observed with all the ligands screened was a general and consistent decrease of the reaction rate, which determines also a degradation of the starting allene during the reaction with a consequent decrement in the final yields. Spirobiindane ligand L_4 gave the best results in terms of yield and enantioselection when the reaction was performed in the presence of 4 Å molecular sieves (entry 5). Under these conditions, tetrahydrocarbazole **14** was obtained in 62 % yield in moderate 70 % ee. The moderate ee's obtained and the lack of chiral ligands with different architectures and low electron-donor abilities prompted us to stop our investigation at the screening level without investigating the scope of the transformation.

With C3 alkyl-substituted 2-vinylindoles **17** we decided to come back to allenamides **4** as dienophiles and tested their reaction under chiral gold(I) catalysis, Scheme 17.

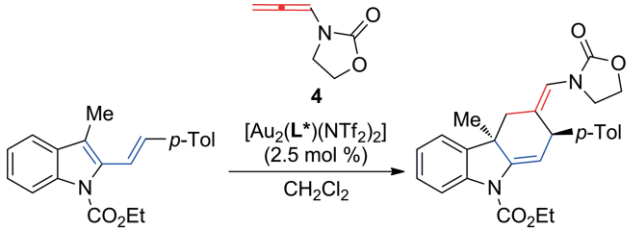
Table 2. Optimization of conditions for the synthesis of **14**.

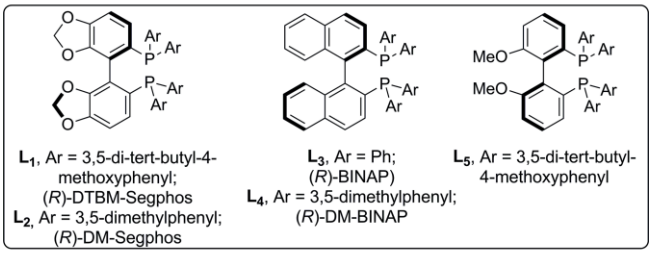


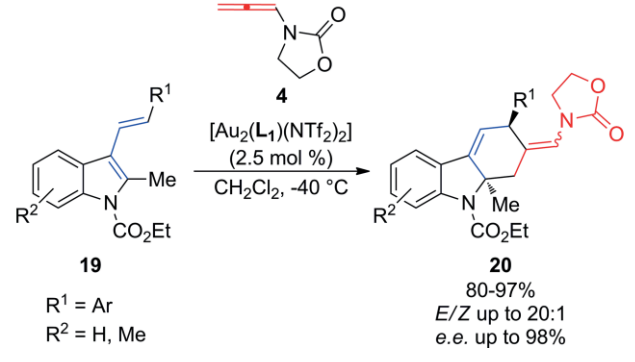
Entry	L*	Additive	Time [h]	Yield [%][a]	*ee*
1	L_1	–	24	90	20
2	L_2	–	24	43	60
3	L_3	–	48	47	62
4	L_4	–	48	42	68
5	L_4	4 Å MS	48	62	70
6	L_5	–	24	33	14



[a] Isolated yields.





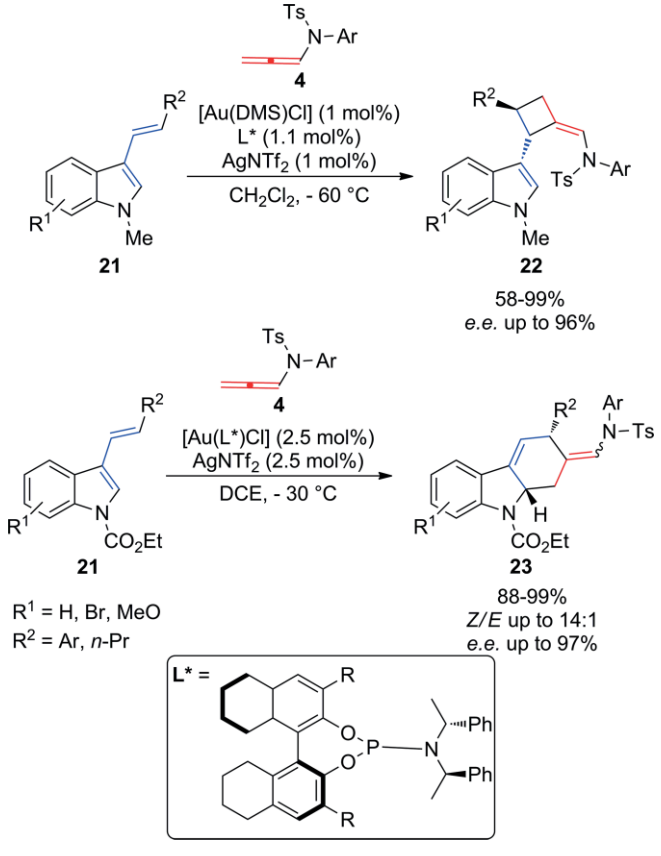


Scheme 17. Gold-catalyzed enantioselective synthesis of carbazoles **18** and **20**.

This reaction would lead to interesting dearomatized tetrahydrocarbazoles **18** bearing a quaternary stereocenter. However, we needed to consider the reduction of nucleophilicity of

a C-3 alkyl-substituted indole and in general of its reactivity due to steric effects. In this case, we based the catalysts screening for the dearomative reaction on the use of diphosphine ligands. In particular, using DTBM Segphos (L_1), under optimized reaction conditions, we obtained the dearomatized carbazole in 85 % yield and in 92 % *ee*. As reported in Scheme 17 other chiral dinuclear gold catalysts gave worst results. Having the optimized conditions, we tested various 3-substituted 2-vinylindoles and the corresponding products were isolated with high yields and generally high enantioselectivities. Switching from allenamides to N-tosylallenamides loss of enantioselectivity was observed. Besides 2-vinylindoles, we briefly expanded the scope of our reaction to 2-methyl-3-vinylindoles **19**. In this case, the reaction afforded the corresponding dearomatized indoles **20** as *E*/*Z* isomers on exocyclic double bond, although in overall excellent yields. After an easy separation on column chromatography, chiral HPLC revealed that both isomers were formed with excellent *ee*.

In 2015, the research group of prof. Zhang reported a comprehensive study on the behavior of 3-vinylindoles **21** in the chiral gold(I) catalyzed reactions with *N*-tosyl allenamides **4**.[28] As reported by us, they observed that the protecting group at the indole nitrogen exerts a deep influence on the reaction outcome. In particular, they found that N-alkyl-substituted indoles give [2+2] cycloadducts **22** whereas N-carbamate protected vinylindoles, [4+2] cycloadducts **23**. Both transformations were realized in their enantioselective versions, Scheme 18.



Scheme 18. Gold-catalyzed enantioselective [2+2] and [4+2] cycloadditions with 3-vinylindoles **21** and allenamides **4**.

At the beginning, they searched for the best reaction conditions to obtain stereoselectively [2+2] cycloadducts and using a phosphoroamidite ligand bearing a saturated cyclohexyl moiety the desired compounds were obtained with ee up to 96 %. Then, [4+2] cycloadditions were realized with the same catalytic system with N-carbamate protected 3-vinylindoles **21** and *N*-tosyl allenamides **4**. Both Z and E isomers of the corresponding tetrahydrocarbazole **23** were isolated in high overall yields and with with ee up to 97 % for the Z isomer and up to 92 % for the E isomer. The author then realized a detailed computational study to understand the origin of the substituent impact on the cycloaddition mode, Figure 2.

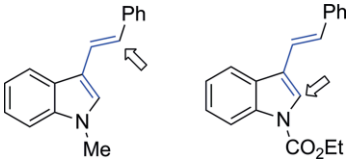
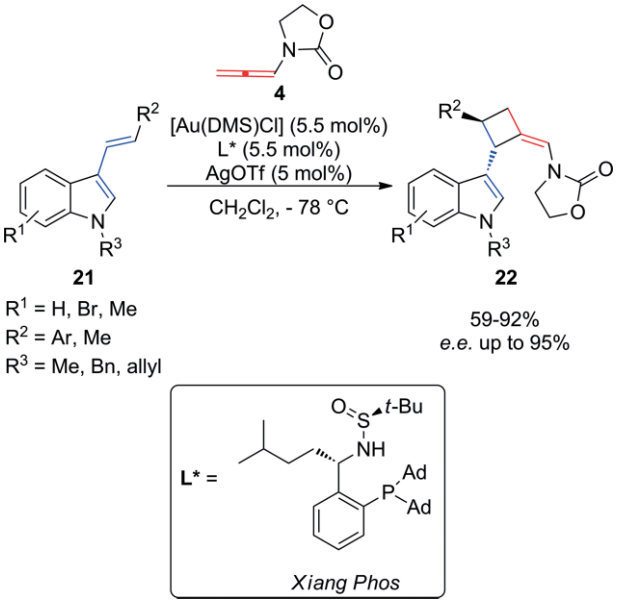


Figure 2. Impact of N-substituent on the reactivity of 3-vinylindoles.

The obtained results are in agreement with theoretical calculation shoving that the most reactive positions towards the addition to electrophilic gold-activated allenamides are those indicated by the arrows in the picture. The exocyclic double bond for [2+2] cycloadditions and the C2 of the indole core for [4+2] cycloadditions. More recently, the same authors extended the [2+2] cycloadditions of 3-vinylindoles **21** to allenamides, Scheme 19.[29]



Scheme 19. Extension of [2+2] cycloaddition of **21** to allenamides.

[2+2] Cycloaddition adducts **22** were obtained in excellent yields and enantioselectivities up to 95 % in the presence of a new Xiang-Phos chiral ligand pertaining to the class of N,P ligands.

Finally, it is worth to underline the behavior of 2-vinylindoles and 3-vinylindoles with allenamides or N-tosylallenamides in [4+2] cycloadditions for the synthesis of the corresponding

tetrahydrocarbazoles. Both diastereo and enantioselective reactions performed with allenamides result in the synthesis of the corresponding tetrahydrocarbazoles with excellent Z selectivity at the exocyclic double bond. On the contrary, a loss of stereoselectivity was observed when *N*-tosylallenamides are involved in the [4+2] cycloadditions. As observed by Professor Zhang, steric factors as well as the nature of substrates, catalysts and reaction conditions could influence the reaction outcome.

3. Reactivity of 4*H*-Furo[3,2-*b*]indoles with Gold-Activated Allenes and Gold Carbenes

Recently, we started exploring the synthesis and the behavior of 4*H*-furo[3,2-*b*]indoles with electrophilic gold-activated π-systems.

4*H*-furo[3,2-*b*]indoles has been seldom reported in the literature for their promising anticancer and anti-inflammatory/analgesic properties.[30] However, the synthesis of 4*H*-furo[3,2-*b*]indoles has been studied essentially in product oriented protocols and their reactivity studied only with regard to simple N- or C2 functionalization reactions.[31] Thus, we synthesized a library of 4*H*-furo[3,2-*b*]indoles **24** adapting, whenever possible, reported methodologies,[31d] Scheme 20.

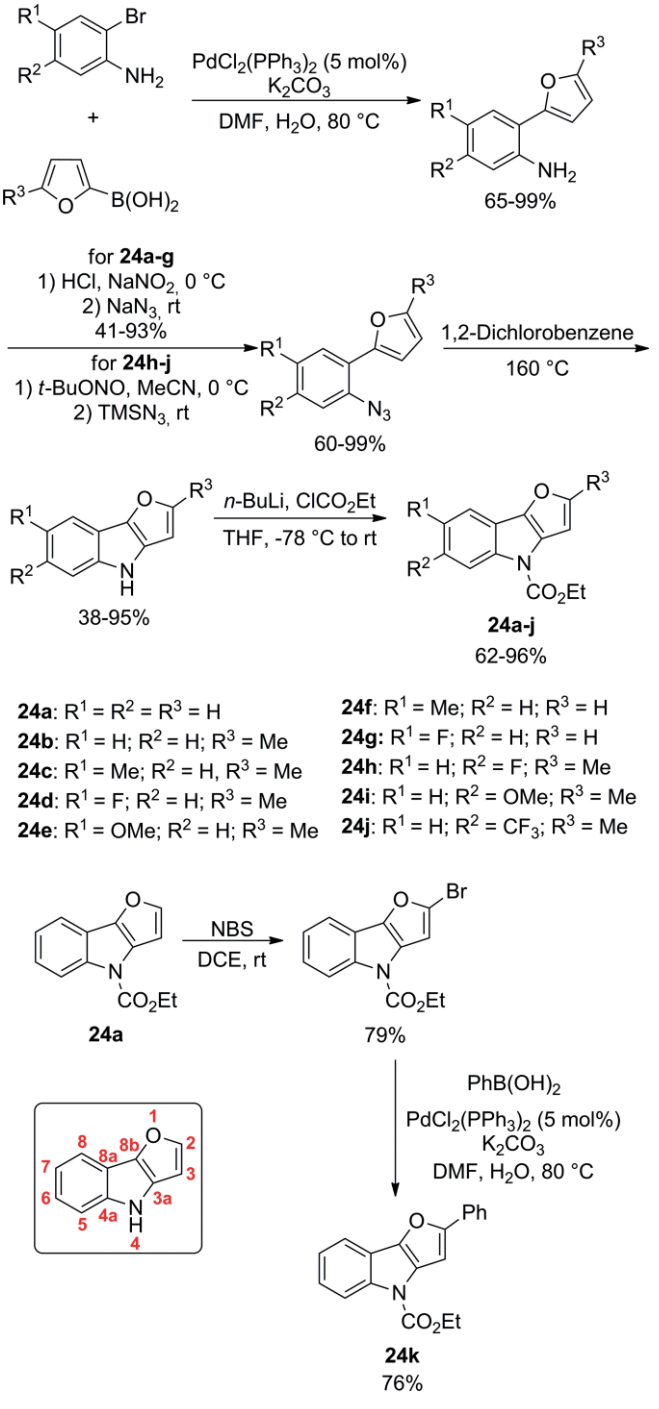
Compounds **24a–j**, substituted at C2 with a hydrogen or a methyl group, were synthesized in a four-step procedure and protected at N4 as carbamate to prevent its functionalization in the presence of electrophilic partners. Compound **24k** bearing a phenyl substituent at C2 was prepared via bromination, followed by Suzuki–Miyaura coupling with phenyl boronic acid.

The 4*H*-furo[3,2-*b*]indole skeleton contains a 4π-system embedded in the rigid framework of a furan ring. Thus, in principle 4*H*-furo[3,2-*b*]indoles could take part as dienes or dienophiles in cycloaddition reactions or participate as electron-rich heterocycles in reactions with electrophiles, Figure 3.

At the beginning of our investigation, by analogy, we checked out the existing literature on the reactivity of the furan ring in these and related reactions, Scheme 21, Scheme 22, Scheme 23, and Scheme 24.

Thus, furans act as dienes in [4+2][32] and [4+3][33] cycloaddition reactions, Scheme 21. Among the most recent examples, in 2019, West and co-workers[32c] reported on the intramolecular [4+2] cycloaddition between in situ generated cyclic allenes **25** with a tethered furan for the synthesis of tetracyclic compounds **26**. Moreover, in 2017, Welch, Harmata and co-workers[33f] realized the intermolecular [4+3] cycloaddition between substituted furans and in situ generated allyl cations **28**. The reaction, performed in the presence of a chiral amino alcohol as catalyst enabled the enantioselective synthesis of tricyclic compounds **29**. In these reactions, the furan ring acts as pure diene. However, there are examples in which the furan ring participates in [4+2][34] and [5+2][35] formal annulation reactions as dienophile through C2–C3 double bond. The primary adducts in turn can undergo furan ring-opening reactions, Scheme 22.

For example, in 2016, Wang and co-workers reported on the hetero-Diels-Alder reactions of furans **27** in a multicomponent process with azoalkenes **30** and water.[34b] The reactions performed in the presence of chiral $CuBF_4$/*t*Bu-Box complex, afforded the corresponding bicyclic compounds **31** as primary



Scheme 20. Synthesis of 4*H*-furo[3,2-*b*]indoles **24a–k**.

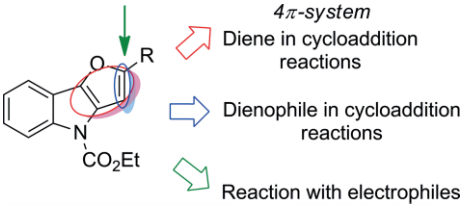
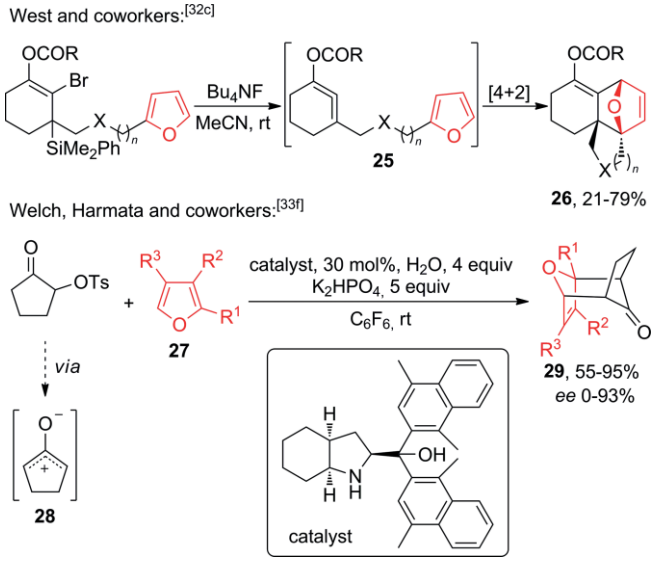
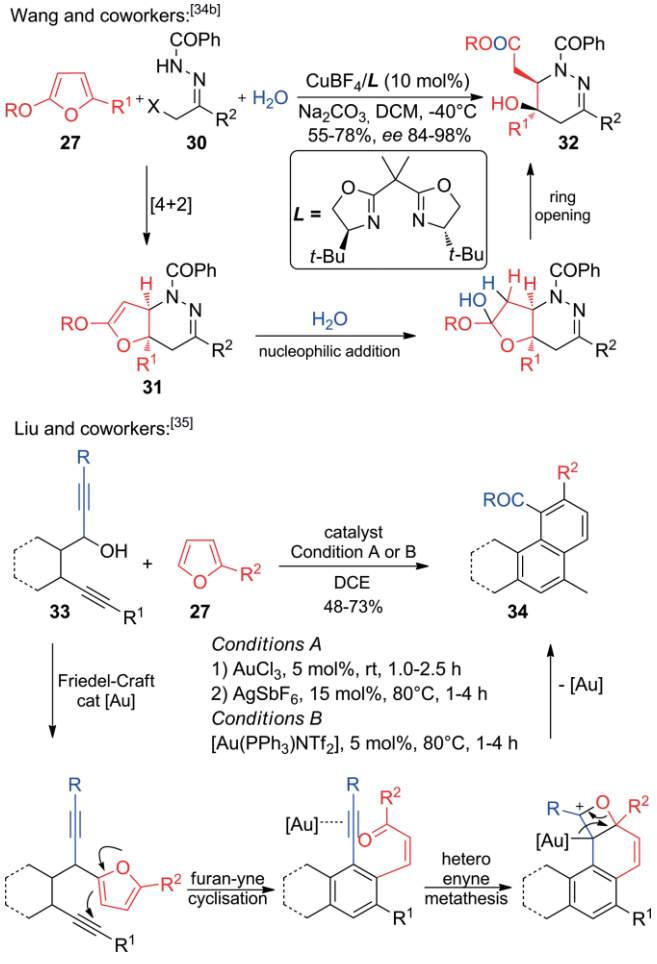


Figure 3. Reactivity of 4*H*-furo[3,2-*b*]indoles.

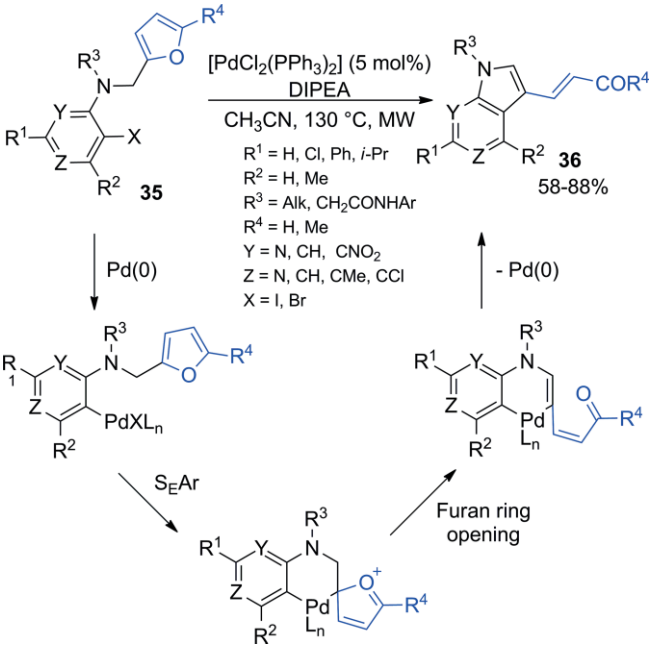


Scheme 21. Furans as dienes in [4+2] and [4+3] cycloaddition reactions.

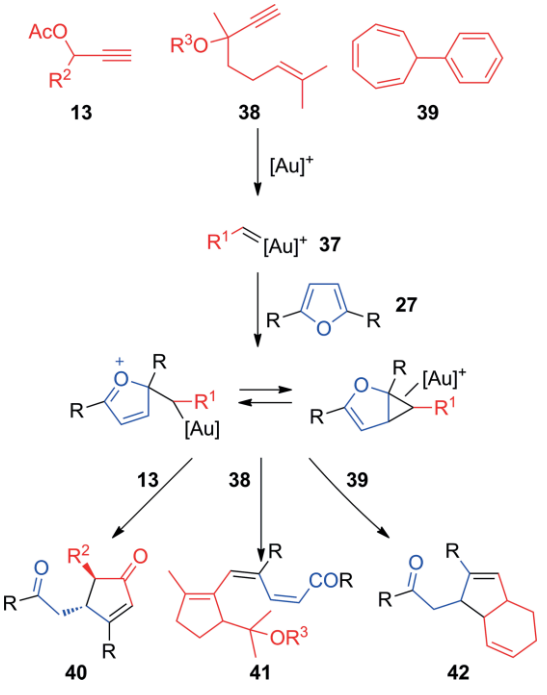


Scheme 22. Furans in formal C2–C3 double bond annulation/ring-opening reactions.

adducts. These latter in the presence of water rearranged by furan ring opening yielding the corresponding tetrahydropyridazines **32** in excellent enantiomeric excesses. A furan ring opening occurs also in the gold-catalyzed cascade reaction between 1,6-diynes **33** and C2 substituted furans **27** for the synthesis of phenanthrene derivatives **34**.[35] The cascade reaction, reported by Liu and co-workers in 2011, involves inter alias a [5+2] furanyne cyclization followed by furan ring rearrangement and hetero enyne metathesis. Finally, the reactivity of furans with electrophilic partners has been investigated in deep and mostly



Scheme 23. Furans in reactions with electrophilic partners, palladium-catalyzed electrophilic aromatic substitution/furan ring opening sequence to give **36**.



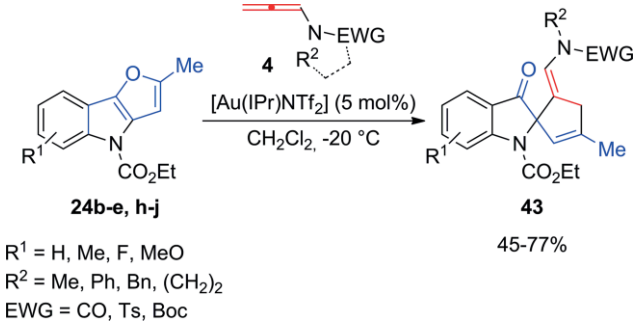
Scheme 24. Furans in reactions with electrophilic partners, reactions between gold(I) carbenes **37** and furans **27**.

involves addition to C2 carbon atom, even when this position is already substituted, followed by a ring opening event.[36] These reactions allow for the installation of α,β-unsaturated carbonyl moieties in a simple and selective manner. In particular, in the field of transition metal catalysis, in 2011, El Kaïm, Grimaud and Wagschal reported a ring opening reaction of furans **35** mediated by a palladium catalyst for the synthesis of α,β-unsaturated aldehydes and ketones tethered to indole moieties **36**, Scheme 23.[37]

Moreover, in the field of gold catalysis, Echavarren and coworkers described the reactivity of furans **27** with gold(I)-carbenes **37** generated in situ from propargyl esters **13**, 1,6-enynes **38** and 7-substituted-1,3,5-heptatrienes **39**, Scheme 24.[38]

All these reactions involve the electrophilic addition of gold(I)-carbenes to furans followed by furan ring opening and give rise, respectively, to cyclopentenones **40**, trienyl-carbonyl derivatives **41** or polycyclic compounds **42**.

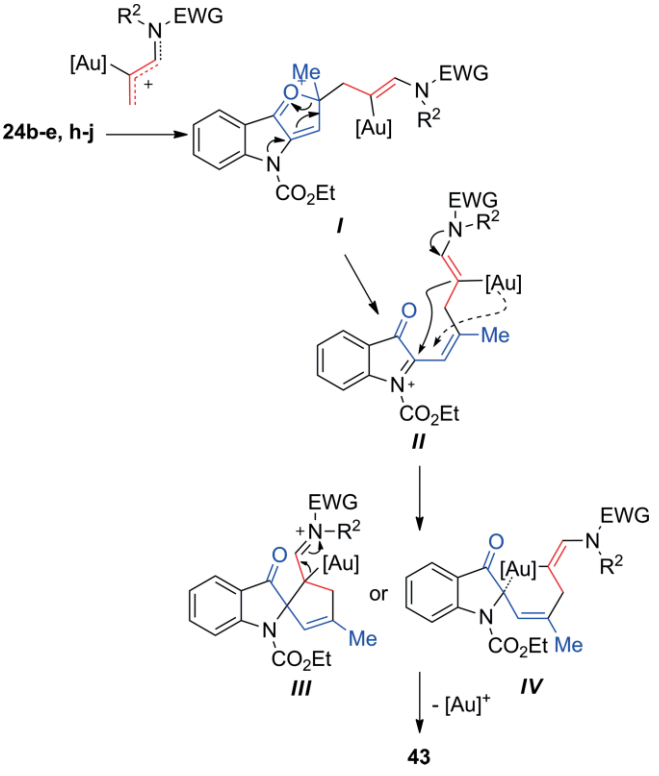
Taking into account these premises, we decided to investigate the reactivity of our newly synthesized 4*H*-furo[3,2-*b*]-indoles **24** with two electrophilic partners both generated in the presence of suitable gold catalysts, namely gold-activated allenamides and gold carbenes. In particular, we realized a new synthesis of 2-spiroindolin-3-ones **43** from 2-methyl-4*H*-furo-[3,2-*b*]-indoles **24b–e, h–j** and allenamides or *N*-tosylallenamides **4** in the presence of a preformed cationic gold(I) complex containing a NHC ligand, Scheme 25.[39]



Scheme 25. Gold-catalyzed synthesis of spiroindolin-3-ones **43** from **24**.

The spiroindolin-3-ones **43** were obtained in good yields with complete stereocontrol at the exocyclic double bond. The choice of the ligand for the gold(I) salt arises from a reaction screening demonstrating that phosphine and phosphite ligands with poorer electron-donor properties than the NHC ligand give rise to the desired compound in lower yields. The reported transformation embodies a new cationic gold(I) catalyzed cascade sequence. Thus, the most plausible reaction mechanism involves addition of a gold-activated allene to the furan moiety of the starting furoindole **24**, affording intermediate ***I***, followed by a ring-opening/ring-closing event, Scheme 26.

In particular, from intermediate ***I*** a rearrangement of the furan ring allows for the formation of iminium indole derivative ***II***. The consequential cyclization of ***II*** followed by elimination of gold(I) provides the final product. The spirocyclization step may be driven from the enaminone system giving rise to intermediate ***III*** or prompted by the formation of the pseudometallacyclic intermediate ***IV*** via electrostatic interaction of gold with indole

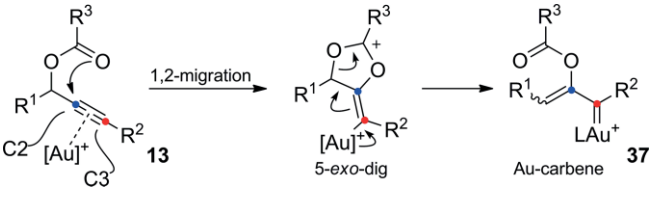


Scheme 26. Proposed mechanism for the synthesis of **43**.

C2. In accordance with several authors we believe that intermediate ***IV*** better explains the stereochemistry at the exocyclic double bond observed in the final products **43**.[40]

From this perspective, in this transformation, the gold catalyst is responsible for both the activation of the allenamide and probably also for the stereocontrol in the spirocyclization event. The limit of this approach resides in the need to operate with C2-substituted furoindoles to avoid the competitive hydroarylation and rearomatization sequence observed when C2-unsubstituted furoindoles were employed as substrates.[39]

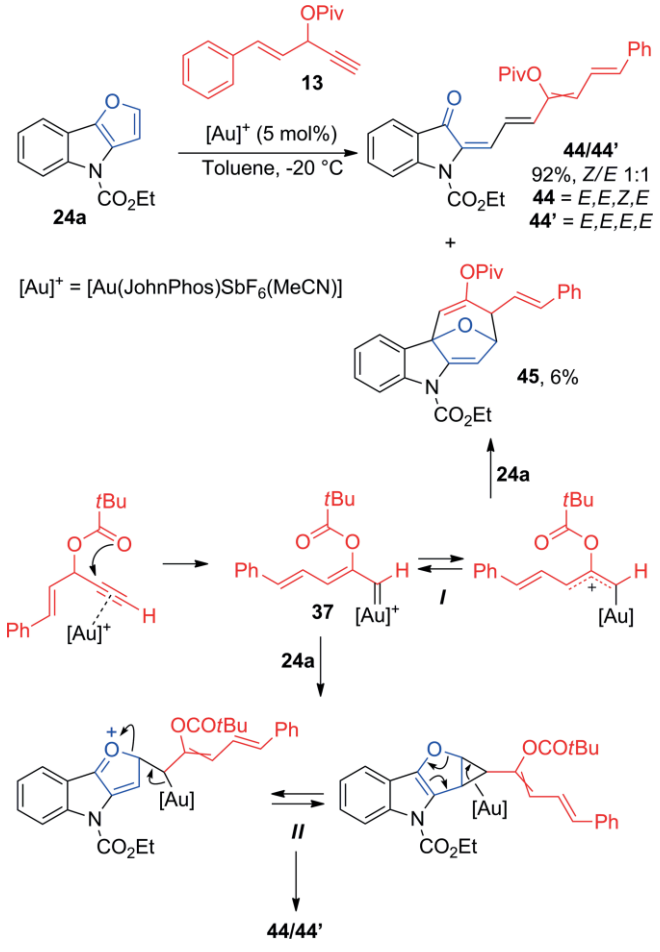
Then, we explored the reactivity of our furoindoles **24** with gold(I)-carbene complexes[41] generated in situ from suitable propargyl esters **13** via gold-catalyzed 1,2-acyloxy migration.[19] As previously mentioned, propargyl esters are useful substrates for cascade reactions. In particular, they are able to generate, via gold-catalyzed 1,3- or 1,2-acyloxy migration, gold-coordinated allenes, Scheme 11, or gold-carbenes **37**, Scheme 27, depending on the substitution pattern.



Scheme 27. Propargyl esters, 1,2-acyloxy migration.

As reported in Scheme 28, a model reaction between furoindole **24a** and propargyl ester **13**, performed in toluene and in the presence of preformed cationic [Au(JohnPhos)(SbF_6)] cat-

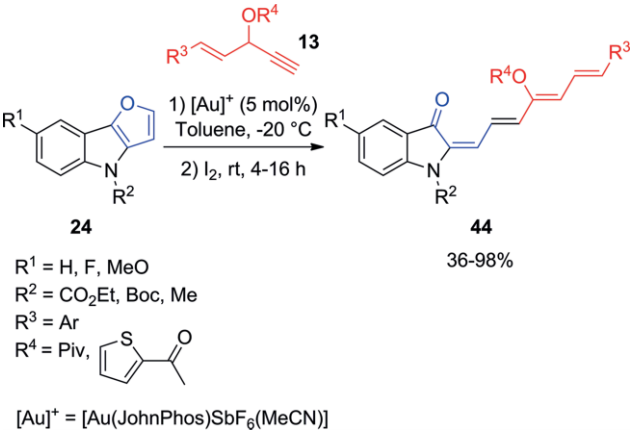
alyst, afforded a separable 1:1 mixture of Z/E 2-(hepta-2,4,6-trien-1-ylidene)-3-oxoindolines **44** and **44′** in overall 92 % yield, besides a 6 % amount of tetracyclic compounds **45**.



Scheme 28. Reactivity of furoindoles **24** with gold(I)-carbenes **37** generated from propargylic ester **13**.

The use of catalysts with different electronic properties resulted in poor yields when a less electrophilic catalyst, [Au(IPr)(NTf$_2$)], was employed or in loss of selectivity toward the formation of the 3-oxoindolines **44/44′** with respect to tetracyclic compound **45** when more electrophilic complexes were employed, [(ArO)$_3$PAu(SbF$_6$)]. The proposed mechanism accounts for the stereochemical outcome of the reaction. Thus, the *E/Z* geometry at the exocyclic trienylidene moiety of 3-oxoindolone is triggered by the hybrid structure of intermediate ***I*** possessing a stable geometry only in the carbene form and dictated by the mechanism of 1,2-migration.[42] However, we observed that isomerization of a mixture of Z/E 3-oxoindolines could be easily achieved in solution and in the presence of catalytic amount of iodine. Thus, performing the reaction as described in Scheme 28 and treating the reaction mixture with iodine at the end of the reaction, we were able to obtain the exclusive formation of the Z isomer, Scheme 29.

At this stage of our investigation, we did not search for the reaction conditions enabling for the synthesis of the tetracyclic compound **45** that probably arises from a [4+3] cyclization pathway in which the gold carbene acts as an oxyallyl cation.



Scheme 29. Scope of the reaction between **24** and **13** under optimized conditions.

Moreover, the obtained compounds complement the already known classes of the 2-methyleneindolin-3-one[43] (indigo derivatives) and 2-allylideneindolin-3-one,[44] representing one of the few example of trienylidene derivatives.[45] Finally, the synthesized 3-indolinones **44** show intense coloration (from yellow to purple) and have been characterized by UV measurements. Once again, as previously outlined for the reaction with allenamides, the reaction takes advantage of the ability of cationic gold(I) catalysts to selectively promote the formation of gold-carbenes from propargyl esters and to promote the electrophilic addition/ring opening sequence with furoindoles demonstrating once again the usefulness of these catalysts in promoting complex cascade reactions under extremely mild reaction conditions.

4. Conclusions

As reported in the introduction, this minireview deals with a particular class of gold catalyzed reactions involving both cyclization and cycloaddition or cascade reactions of indole derivatives for the synthesis of polycyclic and complex compounds. More specifically, the minireview focuses on those reactions involving in the cyclization process an external substituent of the indole moiety as described in Scheme 1b. This minireview consists of two sections dedicated to the chemistry of vinylindoles and furoindoles, respectively. The chemistry of gold catalyzed reactions of vinylindoles comprises essentially [4+2] cycloaddition reactions with *allenes*, preformed or generated in situ, for the synthesis of carbazoles, Table 3.

Excellent levels of diastereoselectivity at the carbazole ring and at the exocyclic double bond of the carbazole moiety have been achieved for 2-vinylindoles with all tested allenes. Whereas reactions developed in the presence of chiral catalysts are less established and are limited to 2-vinylindoles and allenyl esters. Other classes of vinylindoles are less investigated, as reported in Table 3. These remarks are not intended to encourage new investigation just to fill in the table However, several remarks could be done for example on the lack of enantioselective reactions. As outlined in recent outstanding reviews,[46] the three main strategies adopted for the development of gold

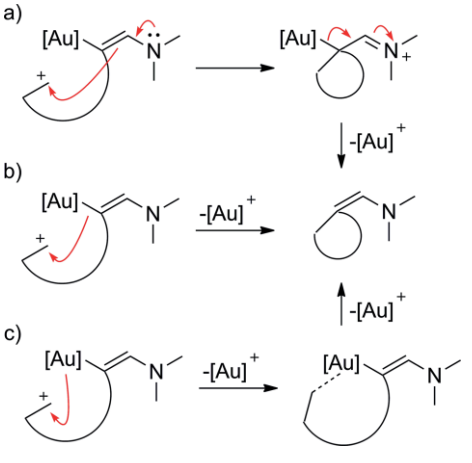
Table 3. [4+2] cycloadditions of vinylindoles with allenes.

Indole	Allenamides Gold(I) catalyst		Allenyl esters Gold(I) catalyst		N-tosylallenamides Gold(I) catalyst	
	Achiral de%	Chiral ee%	Achiral de%	Chiral ee%	Achiral de%	Chiral ee%
2-vinyl	99%	–	99%	70%	99%	–
3-vinyl	99%	–	–	–	–	E 92% Z 97%
2-vinyl-3-methyl	99%	92%	–	–	–	60%
3-vinyl-2-methyl	–	E 84% Z 98%	–	–	–	–

catalyzed enantioselective reactions encompass the use of bimetallic atropoisomeric phosphine ligands, monodentate phosphoroamidite ligands and the use of achiral cationic catalysts coupled with chiral counteranions. The use of these catalysts allowed for the realization of enantioselective transformations mainly based on the activation of alkyne, allene and alkene substrates in inter and intramolecular reactions with nucleophiles for the synthesis of cyclic compounds. However, over the last years, new methodologies in the more general field of transition metal catalysis gained major attention. Inter alias, hybrid catalysts, such as metalloenzymes, realized by including an organometallic catalyst in a host (artificial)protein, find application for efficient enantioselective transformations.[47] These catalysts can be roughly defined as hybrid catalyst competently combining the catalytic activity of transition metals with the ability of the enzymes to create the functional chiral environment through covalent, dative or supramolecular bonds. Besides, metallo-peptides find applications in the same field with the advantage that peptides can be conveniently prepared via automated methodologies.[48] Moreover, application of different type of nanostructures underwent incredible expansion over the last years including in catalysis.[49] The most developed materials include chiral nanostructures mainly organized in nanotube, nanocage and micelles and based on the assembly of small and medium sized molecules. It is worth to mention that, apart from gold(0) nanoparticles, gold metal salts has been little or no included in these studies. The authors suggest referring to the cited specialized literature for deepening. Aside from the study of new catalysts, vinyl indoles deserve attention also in reactions different from classical [4+2] pathways. For example, the achievement of [4+1] cycloadditions could give rise to new carbocyclic and heterocyclic systems. Formal [4+1] gold(I) catalyzed reactions has been reported in the literature.[50] The one carbon unit is mainly provided by gold carbenes, however dienes itself has been never used as four carbons partner. Finally, higher order cycloadditions, such as [4+3] cycloadditions, has been recently described using gold-activated oxy- and aminoallyl cations as three carbons component.[12] This chemistry could furnish the basis for the future development of the chemistry of vinylindoles.

In the second section of this minireview we reported our most recent achievements in the field of gold catalysis. In these works we employed 4*H*-furo[3,2-*b*]indoles as substrates, a class of fused heterocycles that has been never explored in the field of gold catalysis. These substrates comprise a 4π-system similar to that present in the vinylindole structure but merged in a furan system. In the first study, 4*H*-furo[3,2-*b*]indoles were treated with gold-activated allenes affording 2-spiro-3-oxindoles. Thus, 4*H*-furo[3,2-*b*]indoles undergo addition of the electrophilic species followed by a ring opening/ring closing event. The first two steps have been reported also for simple furans for the synthesis of unsaturated carbonyl compounds. In the second study, in the presence of gold carbenes, generated in situ from properly substituted propargylic esters, 2-methylene-3-oxoindoles could be generated through the furan ring rearrangement. However, whereas in the first example only the C2 position of the reacting furoindole is involved in the first step of the reaction, in the second example, both C2 and C3 of the furoindole are involved in the reaction. In both cases, the high levels of selectivity and the mild reaction conditions employed give reason to believe that further expansion of this chemistry can be easily achieved probably by modulation of the reactivity of the 4*H*-furo[3,2-*b*]indoles and by the accurate choice of electrophilic partners. In particular, as already established, substituents at the nitrogen atom induce a profound variation on the electronic properties of the indole moiety and this peculiarity can be exploited for the design of new transformations. We would consider, for example, the involvement of the furan moiety in cycloaddition reaction, in particular [4+3] cycloadditions not yet described for fused furan derivatives.

A final remark is devoted to the reaction mechanisms of all these transformations involving allenes. Most cyclization steps involve intermediates containing a N-C=C-[Au] motif from which the cyclization occurs, see Scheme 7, Scheme 9, Scheme 12, Scheme 15, and Scheme 26. The ring closure can be explained thru diverse mechanisms, Scheme 30.



Scheme 30. Plausible cyclization mode in vinyl-gold intermediates.

Scheme 30a reports a nitrogen assisted ring closure followed by cationic gold(I) elimination. In Scheme 30b a heterolytic fragmentation of the [Au]-C bond delivers the cyclization product. Finally, in Scheme 30c the cyclization step is assisted by gold

via an electrostatic interaction with the electrophilic moiety, resulting in a pseudo-metallacyclic intermediate from which elimination of gold(I) affords the final product. Several computational studies support the mechanisms reported in Scheme 30b[26] and 30c.[12,40] Moreover, both mechanisms better explain the stereoselectivity observed for the exocyclic double bond in the final products. However, when loss of selectivity is observed, for example when *N*-tosylallenamides are employed, an intermediate like that reported in Scheme 30a cannot be excluded.

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Keywords: Gold · Indoles · Allenes · Carbene ligands · Cycloaddition · Homogeneous catalysis

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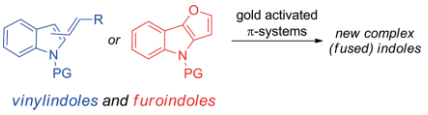
Gold Catalysts



The use of substituted or polycyclic indoles in reactions with gold-activated π-systems allows for the synthesis of new classes of carbazole derivatives and highly functionalized indoles under mild conditions and with high level of regio diastereo and enantio selectivities.

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