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Synthesis of Azocino[5,4-*b*]indoles *via* Gold-Catalyzed Intramolecular Alkyne Hydroarylation

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Abstract: An efficient procedure for the synthesis of the azocino[5,4-*b*]indole framework is presented, relying on a cationic gold-catalyzed intramolecular alkyne hydroarylation of propargylic amides derived from various tryptamines and 3-substituted 2-propynoic acids. The triphenylphosphinegold(I) chloride/silver(I) triflate catalytic system was found to be superior to our previously described mercury(II) triflate catalyst, and hence the substrate scope of the process was significantly expanded.

Keywords: C–C coupling; cyclization; gold catalysis; medium-ring compounds; nitrogen heterocycles

Indole-annulated medium-sized rings are important heterocyclic motifs occurring in both natural and synthetic products. Nitrogen-containing seven- and eight-membered rings are the most widespread[1] and have been constructed employing various methods including intramolecular Friedel–Crafts alkylation,[2] intramolecular radical cyclization,[3] ring-closing metathesis,[3b,4] classical[5] and oxidative[6] Heck reaction, one-pot/tandem processes,[7] multi-component approaches[8] and ring-expansion protocols.[9] We have recently described the assembly of azocino[4,5,6-*cd*]indoles and azepino[4,5-*b*]indoles *via* an intramolecular reductive Heck reaction (formal hydroarylation of the triple bond).[10] The main disadvantage of this method is the difficult accessibility of halogenated indole precursors. Therefore direct hydroarylation of the triple bond might be viewed as an attractive alternative that can provide fast access towards complex indole-fused medium-sized rings starting from easily available precursors.[11]

This concept was for the first time successfully realized by Echavarren and co-workers by applying gold catalysis for the construction of the azepino[4,5-*b*]indole and azocino[4,5-*b*]indole cores.[12] The reaction outcome was shown to be strongly dependent on the nature of the employed gold catalyst. While the strong cationic Au(I) complex (JohnPhosAu-MeCN)SbF_6 gave rise to azepino[4,5-*b*]indoles **1** bearing an exocyclic double bond, $AuCl_3$ generally provided the azocino[4,5-*b*]indoles **2** as the major product along with azepino[4,5-*b*]indoles **3** bearing migrated endocyclic double bond (Scheme 1). Inspired by Echavarren's procedure, we have recently established a microwave-assisted $Hg(OTf)_2$-catalyzed intramolecular alkyne hydroarylation reaction for the synthesis of variously substituted azocino[4,5-*b*]indoles of type **4** (Scheme 1).[13]

Since most of the inorganic and organic mercury compounds are highly toxic, we were searching for an alternative catalytic system to replace $Hg(OTf)_2$ in our process. However, as earlier attempts to employ other Lewis acid catalysts such as AuCl, $AuCl_3$, AgOTf, AgO_2CCF_3, $PdCl_2$ and $PtCl_2$ met with failure,[13] we switched our attention to strong cationic Au(I) complexes.[14] Herein we wish to report our findings in this area and we will give a brief comparison with our previous results.[15]

A combination of monophosphine Au(I) chlorides with various Ag(I) salts is known to produce *in situ* cationic Au(I) species. Therefore we set up a number of small-scale experiments with propargylic amide **5a** and various Au/Ag-catalytic systems in deuterated chloroform allowing direct recording of ^{1}H NMR spectra (Table 1). The application of 5 mol% of $AuPPh_3Cl$/AgOTf resulted in a 100% conversion of **5a** within 4.5 h (Table 1, entry 1). It is worth noting that this reaction was extremely clean as besides the desired product **4a** and phosphine ligand no by-products were observed in the ^{1}H NMR spectrum of the reaction mixture.[16] Application of 5 mol% of Au(X-Phos)Cl/AgOTf resulted in a 91% conversion of **5a** for the same time (Table 1, entry 2). Also the use of 5 mol% of $AuPPh_3Cl/AgSbF_6$ or $AuPPh_3Cl/AgNTf_2$

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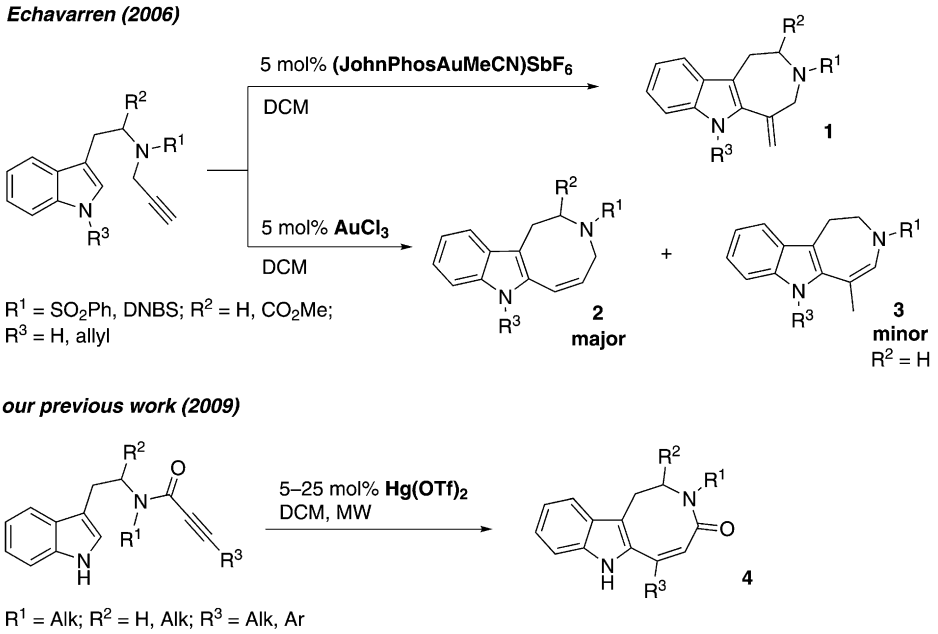
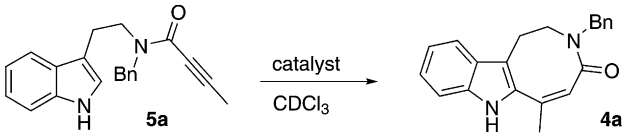


Scheme 1. Various approaches towards azocino[4,5-*b*]indoles and azepino[4,5-*b*]indoles involving an intramolecular hydroarylation of the triple bond.

both led to decreased conversions of 80% and 66% respectively (Table 1, entries 3 and 4). $AuPPh_3Cl$ alone or together with AgO_2CCF_3 resulted in a no conversion of starting propargylic amide **5a** (Table 1, entries 6 and 5). Similarly no conversion was observed when employing 10 mol% of AgOTf at room temperature (Table 1, entry 7), although with moderate heating at 60 °C for 2 h a low conversion of 20% was obtained (Table 1, entry 8). Surprisingly the addition of 20 mol% of triphenylphosphine ligand completely inhibited the above reaction (Table 1, entry 9). We have already mentioned in the previous study that Brøn-

Table 1. Screening of various catalytic systems for the intramolecular alkyne hydroarylation leading to azocino[4,5-*b*]indole **4a**.[a]



Entry	Catalyst	Conditions	Conversion [%][b]
1	5 mol% $AuPPh_3Cl$/AgOTf	r.t., 4.5 h	100[c]
2	5 mol% Au(X-Phos)Cl/AgOTf	r.t., 4.5 h	91[d]
3	5 mol% $AuPPh_3Cl/AgSbF_6$	r.t., 4.5 h	80[d]
4	5 mol% $AuPPh_3Cl/AgNTf_2$	r.t., 4.5 h	66[d]
5	5 mol% $AuPPh_3Cl/AgO_2CCF_3$	r.t., 4.5 h or 50 °C, 2 h	0
6	5 mol% $AuPPh_3Cl$	r.t., 4.5 h or 50 °C, 2 h	0
7	10 mol% AgOTf	r.t., 2 h	0
8	10 mol% AgOTf	60 °C, 2 h	20[e]
9	10 mol% AgOTf/20 mol% PPh_3	60 °C, 7 h	0
10	5 mol% TfOH	r.t. or 60 °C, 2 h	0

[a] Reactions were carried out on a 0.1 mmol scale of **5a** in $CDCl_3$ (0.5 mL).
[b] Determined by ^1H NMR directly after the indicated reaction time with respect to starting propargylic amide **5a**.
[c] Completion of the reaction was first confirmed by TLC.
[d] The relation between the reaction time and conversion is not completely accurate in these cases as reaction still goes during ^1H NMR measurements.
[e] After 2 h the reaction stops presumably due to precipitation of the catalyst as a silver mirror.

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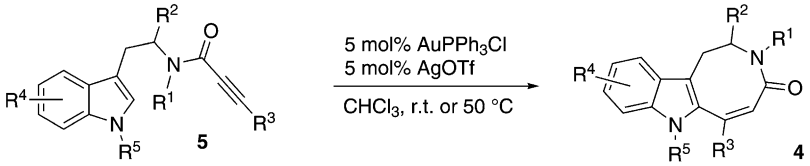
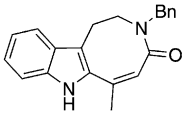
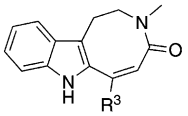
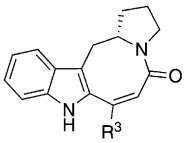
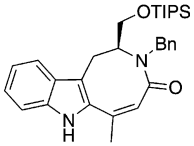
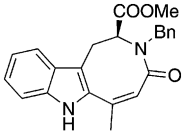
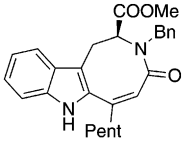
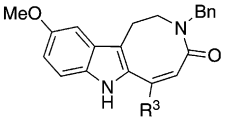
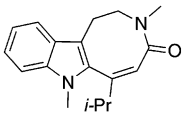
Table 2. Scope of the novel $AuPPh_3Cl$/AgOTf-catalyzed intramolecular alkyne hydroarylation protocol leading to azocino-[4,5-*b*]indoles **4**.



Entry[a]	5	Conditions	Product 4		Yield[b]	Yield with $Hg(OTf)_2$[c]
1	**5a**	r.t., 6 h		**4a**	99	85 (MW) or 95 (conv)
2	**5b**	r.t., 7 h		**4b**, R^3 = Me	92	86
3	**5c**	r.t., 16 h		**4c**, R^3 = *i*-Pr	91	79
4	**5d**	50 °C, 2 h		**4d**, R^3 = Ph	95	61
5	**5e**	50 °C, 2 h		**4e**, R^3 = Me	82	75
6	**5f**	50 °C, 2 h		**4f**, R^3 = Ph	88	58
7[d]	**5g**	50 °C, 20 h		**4g**	72	78
8[d]		50 °C, 8 h			26 (52)[e]	
9[d,f]		50 °C, 38 h			48	
	5h			**4h**		0
10[d]		50 °C, 12 h			10 (21)[e]	
11[d,g]		50 °C, 68 h			27	
	5i			**4i**		–[h]
12[d]	**5j**	r,t,, 22 h		**4j**, R^3 = Me	93	–[h]
13[d]	**5k**	50 °C, 2 h		**4k**, R^3 = Ph	81	–[h]
14 [f]	**5l**	50 °C, 68 h		**4l**	70	–[h]

[a] Reactions were carried out on a 0.4-mmol scale, unless otherwise specified.
[b] Isolated yields.
[c] From ref.[13]
[d] Carried out on a 0.3-mmol scale.
[e] Yields based on recovered starting material are given in parenthesis.
[f] 10 mol% of catalysts were used.
[g] 15 mol% of catalysts were used (added in two portions: first 10 mol% followed by 5 mol% after 16 h).
[h] No data.

sted acids such as CF_3COOH and TfOH are not suitable catalysts for our process.[13] Nevertheless we decided to evaluate reaction with TfOH more precisely since Au/Ag catalytic systems might produce *in situ* small quantities of strong protic acid which could be responsible for the actual catalysis. However no traces of azocino[4,5-*b*]indole **4a** were observed in the reactions catalyzed by 5 mol% of TfOH after 2 h at room temperature or 60 °C (Table 1, entry 10) confirming that our alkyne hydroarylation process is

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most likely catalyzed by cationic Au(I) species. On the basis of this catalyst screening the $AuPPh_3Cl$/AgOTf combination was chosen for the further elaboration.

Next we investigated the scope and limitations of the process. In most cases the $AuPPh_3Cl$/AgOTf catalytic system was found to be superior to the previously described $Hg(OTf)_2$-catalyst delivering target indoloazocines **4** in improved yields (Table 2, entries 1–7). A small drop of the yield was only observed for the reaction with TIPS-*O*-protected propargylic amide **5g** (Table 2, entry 8). The best yield improvement was achieved in the reactions with propargylic amides **5d** and **5f** derived from 3-phenyl-2-propynoic acid (Table 2, entries and 6). More importantly, in case of the reaction with L-tryptophan derivative **5h** where $Hg(OTf)_2$ completely failed, the application of the novel $AuPPh_3Cl$/AgOTf-catalyzed protocol allowed us to obtain the desired indoloazocine **4h** in 26% yield (Table 2, entry 8). This yield could be further increased by applying a higher catalyst loading (10 mol%) and a prolonged reaction time (Table 2, entry 9). Encouraged by this result we decided to test one more L-tryptophan-derived substrate **5i** (Table 2, entries 10 and 11). Similarly to the previous case the yield of the desired indoloazocine **4i** could be improved through increasing the catalyst loading and the reaction time.

Next we decided to extend the applicability of our new protocol to the synthesis of indoloazocines bearing substituents on the indole core. To our great satisfaction, propargylamides **5j**, **k** derived form *N*-benzyl-5-methoxytryptamine could be successfully cyclized employing the standard catalyst loading (5 mol%). The corresponding indoloazocines **4j**, **k** were obtained in good yields of 93% and 81%, respectively (Table 2, entries 12 and 13). Remarkably, substrate **5l** comprising the *N*-methylated indole was also found to be applicable. Carrying out the cyclization with an increased catalyst loading (10 mol%) we were able to synthesize the indoloazocine **4l** in a good yield of 70% (Table 2, entry 14).

On the basis of the substrate scope investigation some general conclusions can be drawn. Propargylic amides **5a–c**, **j** derived from both (3-alkyl)-2-propynoic acids and simple tryptamines ($R^2 = R^5 = H$) could be efficiently converted into the corresponding indoloazocines **4a–c**, **j** employing a standard catalyst loading of 5 mol% at room temperature. However, in the case of the more complex tryptamine/tryptophan derivatives **5e–i**, **l** or 3-phenyl-2-propynoic acid amides **5d**, **f**, **k** a higher reaction temperature of 50 °C and in some cases an increased catalyst loading were needed to achieve an acceptable conversion rate.

Generally, most of the $AuPPh_3Cl$/AgOTf-catalyzed reactions were found to be clean and high yielding with the exception of the L-tryptophan derivatives **5h**, **i**. These reactions were rather sluggish and unclean therefore the corresponding final azocino[4,5-*b*]indoles **4h**, **i** required additional purification by recrystallization after the column chromatography (Table 2, entries 8–11).

In our previous study we have demonstrated that the $Hg(OTf)_2$-catalyzed cyclization of 2-propynoic acid derived propargylic amides **5m**, **n** containing a terminal triple bond in contrast to other substrates proceeds in *exo*-fashion thus resulting in a formation of azepino[4,5-*b*]indoles **6m**, **n** (Table 3, entries 1 and 6).[17] The novel $AuPPh_3Cl$/AgOTf-catalyzed protocol being applied to substrates **5m**, **n** also operated through the *exo*-mode. However, in both cases in addition to azepino[4,5-*b*]indole **6m**/**6n** the formation of considerable amounts of other *exo*-cyclized product, spiro-fused indole derivative **7m**/**7n**, was observed (Table 3, entries 2 and 7). Also in reaction with propargylic amide **5m** a small amount of *endo*-cyclized azocino[4,5-*b*]indole **4m** was detected (Table 3, entry 2).

From the operational point of view, the $AuPPh_3Cl$/AgOTf-catalyzed protocol allowed to achieve full conversion of starting propargylamides **5m**, **n** in 24 h at room temperature (Table 3, entries 2 and 7). Carrying out the $AuPPh_3Cl$/AgOTf-catalyzed cyclization of **5m** at 50 °C shortened the reaction time but did not significantly affect the reaction outcome (Table 3, entry 3). Surprisingly the application of AgOTf (10 mol%) as a sole catalyst at increased temperature of 60 °C not only resulted in unexpectedly[18] high conversions of **5m**, **n** but also changed the mode of cyclization to the *endo*/*exo* competition (Table 3, entries 4 and 8). As a result *endo*-cyclized azocino[4,5-*b*]indoles **4m** and **4n** were isolated and characterized. Furthermore, the precise analysis of the ^1H NMR-spectrum of the reaction mixture (Table 3, entry 4) revealed the formation of *endo*-cyclized spiro-fused indole **8m**.[16] The addition of 20 mol% of triphenylphosphine ligand returned the AgOTf-catalyzed reaction into the *exo*-mode and again dramatically slowed down the general cyclization rate (Table 3, entry 5).

Formation of spiro cyclized indoles **7** and **8** might be considered as an indirect evidence for the mechanism (Scheme 2) which was previously proposed by Echavaren for the similar process. The triple bond activated by the metal catalyst first reacts with the 3rd, the most reactive, position of the indole core *via exo*- or *endo*-mode resulting in the formation of spiro-fused intermediates **A** or **B**, respectively. Subsequent proton transfer in these intermediates could provide **7** and **8** with concomitant demetalation. However, more commonly **A**/**B** further rearranges into **C**/**D** by a 1,2-shift followed by formation of the ring expanded product **6**/**4**. The terminal character of the reacting triple bond in the propargylic amides **5m**, **n** seems to be a crucial factor facilitating the *exo*-mode of pro-

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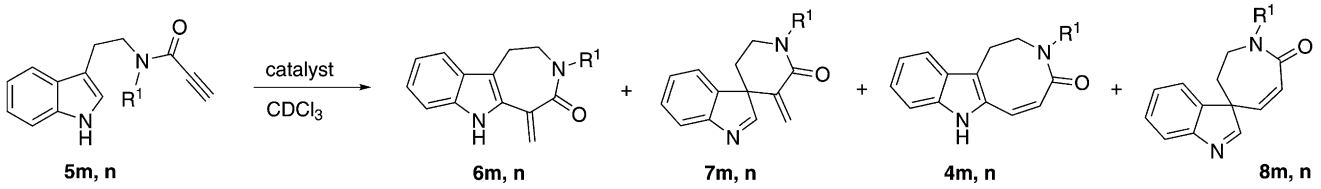
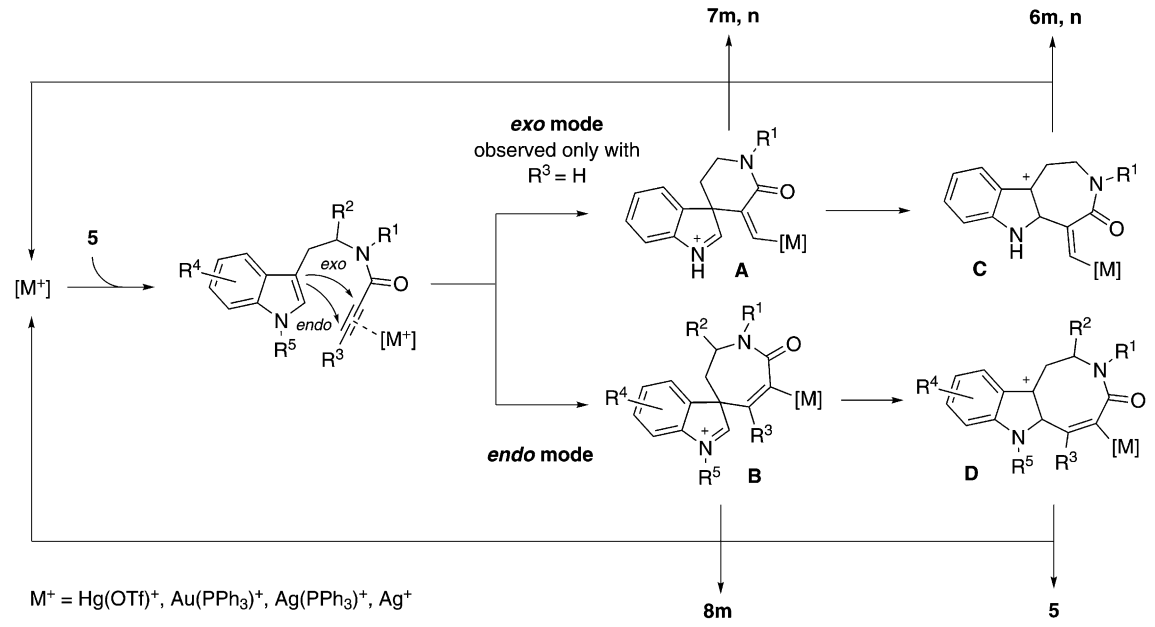
Table 3. Cyclization of propargylic amides **5m**, **n** containing the terminal triple bond.



Entry[a]	5	Catalyst; Conditions	Yield[b]			
			6	**7**	**4**	**8**
1[c]	**5m**, R^1 = Me	5 mol% $Hg(OTf)_2$; 50 °C, 48 h, CH_2Cl_2	21	nd[d]	nd[d]	nd[d]
2		5 mol% $AuPPh_3Cl/AgOTf$; r.t., 24 h, $CHCl_3$ ($CDCl_3$)	24 (25)[e]	15 (30)[e]	–[f] (4)[e]	nd[d]
3[g]		5 mol% $AuPPh_3Cl/AgOTf$; 50 °C, 7 h, $CDCl_3$	–[f] (25)[e]	–[f] (29)[e]	–[f] (5)[e]	nd[d]
4		10 mol% AgOTf; 60 °C, 6 h, $CHCl_3$ ($CDCl_3$)	9 (10)[e]	7 (23)[e]	29 (31)[e]	–[f] (2)[e]
5[g,h]		10 mol% AgOTf/20 mol% PPh_3; 60 °C, 6 h, $CDCl_3$	nd[d]	–[f] (9)[e]	nd[d]	nd[d]
6[c]	**5n**, R^1 = Bn	5 mol% $Hg(OTf)_2$; 50 °C, 48 h, CH_2Cl_2	25	nd[d]	nd[d]	nd[d]
7		5 mol% $AuPPh_3Cl/AgOTf$; r.t., 24 h, $CHCl_3$ ($CDCl_3$)	25 (26)[e]	25 (30)[e]	nd[d]	nd[d]
8[i]		10 mol% AgOTf; 60 °C, 6 h, $CHCl_3$ ($CDCl_3$)	–[f] (4)[e]	–[f] (5)[e]	14 (21)[e]	nd[d]

[a] Reactions were carried out on a 0.4-mmol scale, unless otherwise specified.
[b] Isolated yields.
[c] From ref.[13] (carried out on a 0.6-mmol scale).
[d] nd = not detected.
[e] Yields in parenthesis are determined by ^{1}H NMR from the corresponding 0.1-mmol scale reaction in $CDCl_3$ using 3,4,5-trimethoxybenzaldehyde as internal standard.
[f] Not determined.
[g] Carried out on a 0.1-mmol scale.
[h] No full conversion of **5m** was achieved; 70% remained unreacted as was determined by ^{1}H NMR.
[i] No full conversion of **5n** was achieved; 19% remained unreacted as was determined by ^{1}H NMR.

cess. This could be ascribed to the fact that the metal activator [M^+] tends to coordinate closer to the terminal carbon of the triple bond. The *endo*-mode for substrates **5m**, **n** could be partially realized only with AgOTf catalyst since Ag^+ in contrast to bulkier Hg-$(OTf)^+$, $Au(PPh_3)^+$ and $Ag(PPh_3)^+$ apparently does not differentiate between triple bond carbons. Conjugation of the triple bond with an electron-withdrawing amide group on the other hand seems to be less strong factor as it does not promote attack of indole



Scheme 2. Mechanistic consideration of the process.

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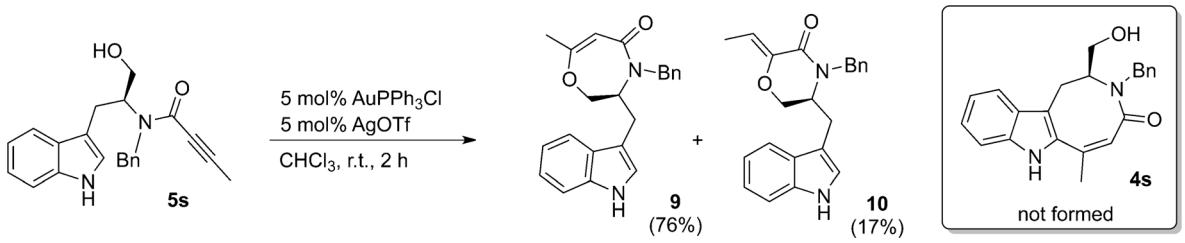

Scheme 3. Regioselective $AuPPh_3Cl$/AgOTf-catalyzed intramolecular hydroalkoxylation of propargylic amide **5r**.

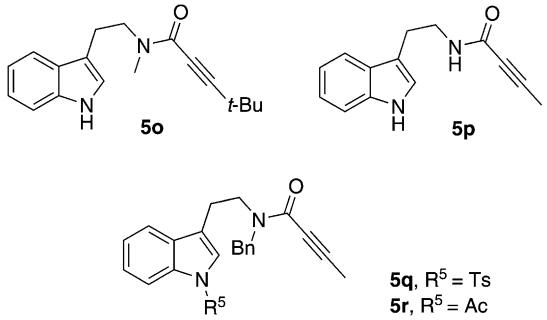

Figure 1. Unsuitable substrates for the $AuPPh_3Cl$/AgOTf-catalyzed process.

in *endo*-fashion in case of $Hg(OTf)_2$-, $AuPPh_3Cl$/AgOTf- and AgOTf/PPh_3-catalyzed cyclizations of **5m**, **n**.

Unfortunately, we were not able to overcome all limitations of the $Hg(OTf)_2$-catalyzed procedure. Thus, propargylic amide **5o** derived from *N*-methyltryptamine and 3-*tert*-butyl-2-propynoic acid, remained unreacted under the novel $AuPPh_3Cl$/AgOTf-catalyzed conditions as well, presumably due to the bulkiness of the *t*-Bu group. Secondary propargylic amide **5p** and propargylic amides **5q**, **r** with an *N*-tosylated or *N*-acylated indole were also confirmed to be unsuitable substrates for our hydroarylation process (Figure 1). However, one of the previously unreactive substrates – **5s** containing an unprotected hydroxy group – was found to possess other interesting reactivity (Scheme 3). Being subjected to the $AuPPh_3Cl$/AgOTf-catalyzed procedure propargylic amide **5s** did not provide the expected azocino[4,5-*b*]indole **4s**.[19] Instead an oxazepine **9** (major product) was formed along with the corresponding six-membered morpholine **10** (minor product). Of course, this result was not completely surprising considering the known reactivity of oxygen nucleophiles in Au-catalyzed additions to C≡C triple bonds.[20] Nevertheless this novel process might be anticipated as a convenient and selective entry to the oxazepine core.

In summary, we have identified the $AuPPh_3Cl$/AgOTf catalytic system as an efficient replacement for the $Hg(OTf)_2$ catalyst in our previously developed intramolecular alkyne hydroarylation reaction leading to azocino[5,4-*b*]indoles. A significant substrate scope expansion was achieved by the application of some previously unreactive substrates and substrates bearing additional substituents on the indole core. A close look at the reactions with terminal propargylic amides resulted in the isolation and characterization of novel cyclized products interesting for the mechanistic understanding of the process. The intramolecular hydroalkoxylation reaction leading to oxazepines is currently under investigation in our laboratory and results will be reported in due course.

Experimental Section

Full experimental details and spectroscopic data for all new compounds along with the copies of ^1H and ^{13}C NMR spectra are available as Supporting Information.

General Procedure for the $AuPPh_3Cl$/AgOTf-Catalyzed Intramolecular Alkyne Hydroarylation (Table 2)

Propargylic amide **5** (0.4 mmol) was dissolved in dry $CHCl_3$ (2 mL). Subsequently AgOTf (5 mg, 0.02 mmol) and $AuPPh_3Cl$ (10 mg, 0.02 mmol) were added. The reaction mixture was allowed to stir at room temperature or 50 °C for the indicated period of time in a sealed screw-cap vial under air atmosphere. The resulting reaction mixture was subjected to column chromatography to give the desired azocino[4,5-*b*]indole **4**.

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