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Homogenous Catalysis

Self-Relay Gold(I)-Catalyzed Pictet–Spengler/Cyclization Cascade Reaction for the Rapid Elaboration of Pentacyclic Indole Derivatives

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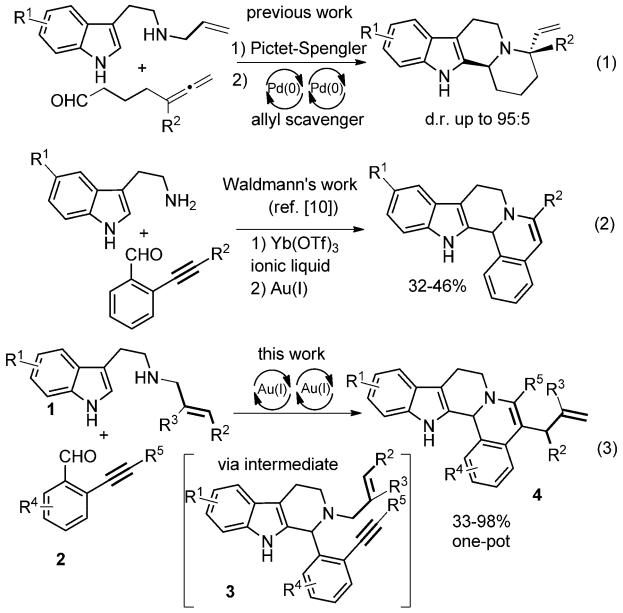
Abstract: Gold-catalyzed cascade reactions allow the rapid elaboration of pentacyclic indolo[2,3-*a*]quinolizidines from *N*-allyl tryptamines and *ortho*-alkynylarylaldehydes. The tandem process combines a gold-catalyzed Pictet-Spengler reaction and a cyclization occurring concomitantly with an allyl transfer from the nitrogen atom to the stilbene function. Various substituted allyls were successfully transferred, furnishing the products in yields typically ranging from 60–98% in high diastereoselectivity. Tryptamines bearing a butenol chain undergo an additional cyclization to chiral hemiaminals in high diastereoselectivities.

The development of tandem catalysis strategies fastens the discovery for new reactions and the elaboration of molecular complexity, by performing several steps in one single flask.[1] Such processes can be the result of several steps concurrently catalyzed by the same catalyst by self-relay catalysis (also known as autocatalysis) or, alternatively, by the combination of two catalysts, in an orthogonal manner, each of which being responsible for the catalysis of one single step.[2] Tandem catalysis is, however, a challenging approach since catalysts and substrates should be compatible to ensure efficient conversion in the desired product and avoiding side reactions. Gold complexes have emerged over the last decade as powerful tools for the synthesis of functionalized molecules.[3] In addition, the gold tolerance to oxygen, moisture, and many functional groups is very high, and make this metal an ideal candidate for the development of tandem catalytic processes, either in orthogonal catalysis with Brønsted acid,[4] or self-relay catalysis.[5] Hence numerous gold complexes have been used in elegant cascade reactions developed for the synthesis of complex compounds by both approaches.[6,7]

Recently, we used allenals as bifunctional key building blocks[8] for the synthesis of polycyclic indolic chiral architectures (Scheme 1, Eq. (1)).[8b,c] The strategy relied on a two-steps sequence consisting of an asymmetric phosphoric acid catalyzed Pictet–Spengler reaction[9] followed by a self-relay palladium-catalyzed cyclization, featuring both the deallylation and the cyclization steps, leading to polycyclic compounds. Very recently, Waldmann and Kumar reported a two-step approach consisting in an $Yb(OTf)_3$-catalyzed Pictet–Spengler reaction followed by a Au^I-catalyzed hydroamination leading to pentacyclic derivatives in moderate yields (Scheme 1, Eq. (2)).[10]



Scheme 1. Previous approaches and proposed work.

For our part, we hypothesized that a gold-catalyzed cascade combining a Pictet–Spengler reaction between *N*-allyltryptamines **1** and *o*-alkynylarylaldehydes **2** and a cyclization with a concomitant allyl transfer from intermediate **3** would lead to analogous polycyclic derivatives **4** in a very rapid one-pot process (Scheme 1, Eq. (3)). The allyl group, which is in general considered a protecting group, would therefore be converted into a three-carbon synthon, potentially useful for further synthetic transformations. Such carboaminations of *N*-allyl nucleophiles on alkynes proceeding with an allyl transfer are known to be very efficient and have led to a variety of heterocycles.[11,12]

In this paper we thus report our efforts in the development of this cascade reaction leading to pentacyclic indolo[2,3-*a*]quinolizidines[13] **4**, in a self-relay Au^I-catalyzed sequence.

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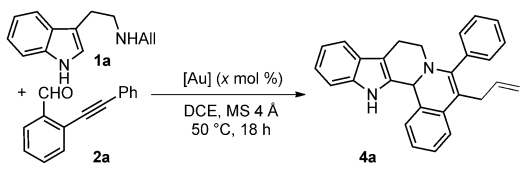
Table 1. Optimization of reaction conditions.[a]



Entry	[Au] (mol%)	Ratio **1**/**2** [mol]	Yield **3a** [%]	Yield **4a** [%]
1	**5a** (5)/DPP (5)	1:2	0	80
2	**5a** (5)	1:2	4	78
3	**5b** (5)	1:2	35	15
4	**5c** (5)	1:2	8	84
5	**5d** (5)	1:2	34	57
6	**5e** (5)	1:2	64	24
7	$AuCl_3$ (5)	1:2	36	11
8	$AuCl_3/AgPF_6$ (5)	1:2	92	8
9	**5c** (5)/DPP (5)	1:2	0	94
10	**5c** (5)	1:2	0	93[b]
11	**5c** (2)	1:2	75	20

[a] Yields measured by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as the internal standard. [b] The yield dropped to 60% when the reaction was performed in the absence of molecular sieves.

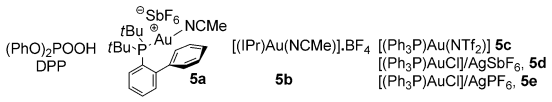
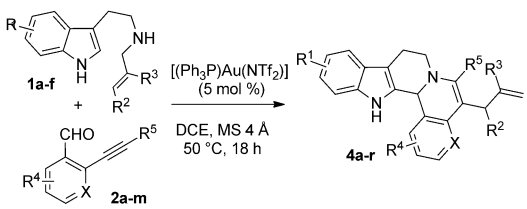


Table 2. Scope of the tandem gold(I)-catalyzed process.[a]



Entry	R^1	R^2	R^3	R^4	R^5	Yield [%][b]
1	H	H	H	H	Ph	**4a**, 97
2	5-OMe	H	H	H	Ph	**4b**, 72
3	5-F	H	H	H	Ph	**4c**, 86
4	6-OMe	H	H	H	Ph	**4d**, 91[c]
5	H	H	H	H	*n*Bu	**4e**, 82
6	H	H	H	H	$SiMe_3$	**4f**, 98
7	H	H	H	H	3-pyridine	**4g**, 62
8	H	H	H	H (X = N)	Ph	**4h**, 72
9	H	H	H	H	$pMeO_2CC_6H_4$	**4i**, 94[c]
10	H	H	H	H	$mOMeC_6H_4$	**4j**, 75
11	H	H	H	5-NO_2	Ph	**4k**, 69
12	H	H	H	5-F	Ph	**4l**, 76
13	H	H	H	6-F	Ph	**4m**, 89
14	H	H	H	5-OMe	Ph	**4n**, 77
15	H	H	H	5-OMe	$pMeO_2CC_6H_4$	**4o**, 97
16	H	H	H	5-OMe	$mOMeC_6H_4$	**4p**, 33
17	H	H	Me	H	Ph	**4q**, 60
18	H	Ph	H	H	Ph	**4r**, 88[d]

[a] Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), **5c** (5 mol%), molecular sieves (4 Å, 100 mg), solvent (1.5 mL). [b] Isolated yields. [c] Reaction performed using the conditions of Table 1, entry 9. [d] d.r. > 95:5.

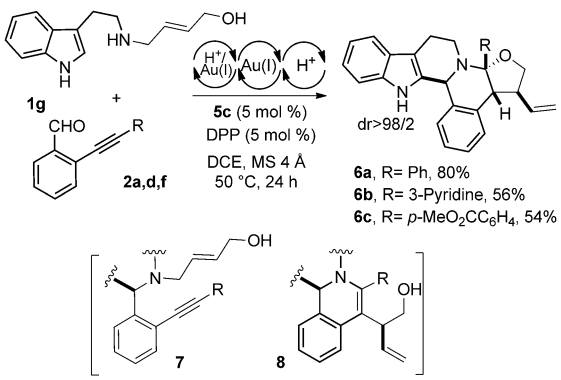
We initiated our study by establishing the suitable catalytic system for the Pictet–Spengler gold-catalyzed cyclization one-pot process (Table 1).

To this aim, *N*-allyl tryptamine **1a** and aldehyde **2a** were reacted in the presence of catalytic amounts of diphenyl phosphate (DPP, 5 mol%),[14] to ensure catalysis of the Pictet–Spengler reaction and Echavarren catalyst **5a** (5 mol%), in dichloroethane at 50 °C. Product **4a**, stemming as expected from a one-pot Pictet–Spengler reaction and gold-catalyzed cyclization was obtained in 80% yield (Table 1, entry 1). Pictet–Spengler reactions can be catalyzed by Au^I or Au^{III} complexes, though their utilization in this reaction is scarce.[15] Indeed, the reaction performed with **5a** as the sole catalyst furnished product **4a** in 78% yield (entry 2), showing the ability for Au^I to catalyze the Pictet–Spengler step. The carbene complex $[(IPr)Au(MeCN)]\cdot BF_4$ (**5b**) led to a mixture mainly composed of the intermediate tetrahydro-β-carboline **3a** (entry 3), while the stable cationic catalyst $[(Ph_3P)Au(NTf_2)]$[16] (**5c**) enhanced the yield of **4a** to 84% (entry 4). The use of catalysts **5d**,**e** and Au^{III} catalysts dropped the yield of **4a** (entries 5–8). The catalyst **5c** was then selected for the following of the study and it was checked whether the addition of DPP (5 mol%) would be beneficial to the reaction. Though the yield increased to 94% (entry 9), the effect of DPP was considered moderate and further optimization was performed with Au^I as the sole catalyst. The ratio between **1a**/**2a** was then optimized to 1.2:1 which allowed an excellent yield and facilitated the purification process (entry 10). A decrease of the catalyst loading to 2 mol% of $[(Ph_3P)Au(NTf_2)]$ dropped the yield to 20% (entry 11).

The scope and the limitations of the reaction were next studied, to determine in particular the influence of the substituents introduced on the aryls on the reactivity in this tandem process (Table 2). Numerous *o*-alkynylarylaldehydes **2** were reacted with tryptamines **1** in the presence of $[(Ph_3P)Au(NTf_2)]$ (**5c**). We first studied the influence of the substituent present on the indole ring and found that both electron-withdrawing (EWG) and -donating groups (EDG) R^1 groups have little influence on the reactivity, furnishing the corresponding products **4a**–**d** in good to excellent yields (Table 2, entries 1–4). The reaction was next successfully performed using alkynes substituted by either alkyl or silyl groups, furnishing the corresponding products **4e** and **4f** in 82 and 98% yields, respectively (entries 5 and 6). The sequence was also compatible with the use of basic heterocyles. Reactions performed with pyridyl groups on either R^5 or with X = N furnished the corresponding heterocycles in 62 and 72% yields, respectively (Table 2, entries 7 and 8).[17] Different functions were next introduced on the aryl moieties at the R^4- and R^5-positions. The reaction proceeded well with EWG or EDG groups at R^5 (entries 9 and 10). Substitution on the arylaldehyde using a nitro functionality led to compound **4k** in a good 69% yield (entry 11). Fluoro derivatives similarly afforded the corresponding compounds **4l** and **4m** (entries 12 and 13). Electron-rich aryl groups were next used successfully in combination with a Ph- or a *p*-CO_2Me-substituted R^5 group (entries 14 and 15). A good 77% yield was obtained with R^5 = Ph (entry 14), increasing to 97% in compound **4o** with an electron-poor R^5 group (entry 15). However, the yield in **4p** dropped to 33% with R^5 =

m-$OMeC_6H_4$ (entry 16), showing that combined electron-donating effects are detrimental to the reaction. Overall it is clear that the reaction is strongly favored with electron-poor substituents, likely by impoverishing the triple bond, thereby increasing its electrophilicity. The migratory ability of various allyl groups was next studied. Reaction of tryptamines **1e–f** functionalized by a methallyl or a cinnamyl group were reacted with aldehyde **2a** in the presence of catalyst **5c.** The corresponding compounds **4q** and **4r** were obtained in good 60 and 88% yields (entries 17 and 18). The relative stereochemistry of **4r**, obtained as a sole diastereomer, was assessed by X-ray crystallography (see the Supporting Information).

We finally evaluated the migratory ability of the (*E*)-4-hydroxybut-2-en-1-yl group of tryptamine (**1g**), possessing a free hydroxyl function (Scheme 2). The reaction of **1g** with aldehyde **2a** in the presence of **5c** (5 mol%) furnished the expected cyclized product **8a** which, upon chromatography on silica gel, evolved partially to the chiral hemiaminal hexacyclic compound **6a**. The use of DPP (5 mol%) as an additional acidic catalyst furnished directly compound **6a** in 80% yield, as a single isomer for which relative stereochemistry was attributed both by nOe and X-ray crystallography studies (Figure 1).



Scheme 2. Orthogonal catalysis to hemiaminals **6**.

This compound is the result of a cascade process, catalyzed both by the Au^I complex and the phosphoric acid, including the Pictet–Spengler/cyclization/allyl migration/hemiaminalization reactions. A point to note is that a stereogenic quaternary center is created within the process and controlled with full diastereoselectivity. The same reaction was performed using aldehydes **2d** and **2f**, furnishing the corresponding compounds **6b** and **6c** in 56 and 54% yields. This complex process allows the formation of four stereogenic centers, three of them being contiguous, in one single synthetic step and in high diastereocontrol.

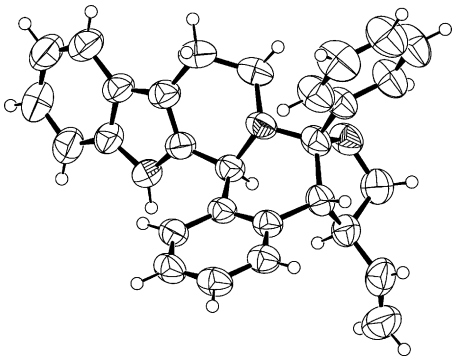
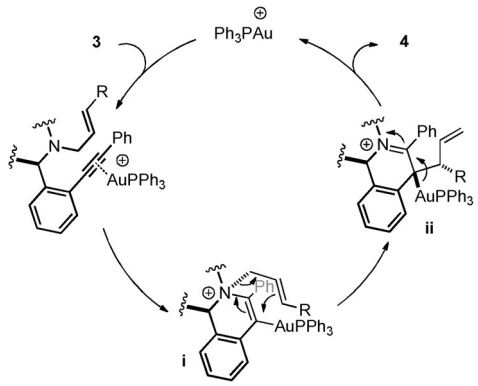


Figure 1. Ortep drawing for compound **6a**.

The mechanism of this gold-catalyzed transformation and in particular its exquisite stereocontrol is worth considering. The migration of an allyl group from a heteroatom to an alkyne function in the course of a gold-[11,12] or platinum-catalyzed[18] process has been previously reported. A dissociative mechanism is proposed in the case of an allyl transfer from an oxygen atom,[12a–d] but it is usually recognized that a concerted pathway is operating from *N*-allyl functions,[11] by an aza-Claisen reaction. The mechanistic pathway of our transformation can be postulated as follows (Scheme 3). After the Pictet–Spengler step catalyzed by Au^I, complexation of the intermediate tetrahydro-β-carboline **3** with the gold catalyst triggers the cyclization by addition of the amine function to the activated triple bond, leading to a quaternary ammonium (**i**). It then undergoes a [3,3]-sigmatropic suprafacial aza-Claisen reaction leading to intermediate (**ii**), with the generation of an additional stereogenic center in high diastereoselectivity when $R \neq H$. The deauration step releases the product **4**. Such a level of diastereoselectivity in the allyl transfer is characteristic of a concerted intramolecular migration. A dissociative migration that would proceed by an allyl cation would on the contrary result in low diastereoselectivity and potentially low regioselectivity (mixture of branched and linear compounds).



Scheme 3. Mechanistic hypothesis (counterions have been omitted for clarity).

In conclusion, we have developed a rapid access to pentacyclic indolic derivatives **4** from *N*-allyltryptamines **1** and *o*-alkynylaryladehydes **2**. The route features a tandem gold-catalyzed Pictet–Spengler reaction and a cyclization proceeding with concomitant allyl migration. The scope of this multicatalytic pathway is wide and allows the fast elaboration of molecular complexity. Tryptamines bearing substituted allyl groups led to the corresponding cyclized derivatives with a high level of dia-

stereoselectivity (>95:5). In particular, with tryptamines bearing a (*E*)-4-hydroxybut-2-en-1-yl group, the reaction undergoes a fully stereoselective additional cyclization to furnish hexacyclic chiral hemiaminals **6** by an orthogonal three-step catalytic sequence using both gold and Brønsted acid catalyses. A point to note is that this process has been performed on deprotected indolic compounds. Current efforts are being directed to the development of an asymmetric version of this multistep sequence.

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Keywords: cascade reaction · gold catalysis · homogenous catalysis · indoles · nitrogen heterocycles

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