Gold-Catalyzed Cascade Reactions of 4*H*-Furo[3,2-*b*]indoles with Propargyl Esters: Synthesis of 2-Alkenylidene-3-oxoindolines

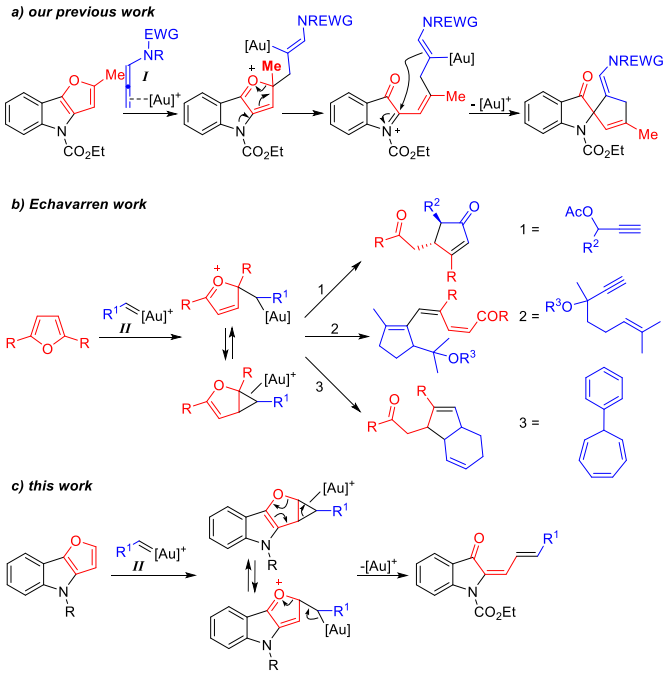
Elisa Brambilla, *[a] Valentina Pirovano, [a] Matteo Giannangeli, [b] Giorgio Abbiati, [a] Alessandro Caselli, [b] and Elisabetta Rossi, *[a]

a. Dipartimento di Scienze Farmaceutiche - Sezione di Chimica Generale e Organica "A. Marchesini", Università degli Studi di Milano, Via Venezian 21, 20133 Milano, Italy.
b. Dipartimento di Chimica and ISTM-CNR, Università degli Studi di Milano, Via Golgi 19, 20133 Milano, Italy.

2-alkenyliden-indolin-3-ones were synthesised in high yields *via* a cascade reaction between 4*H*-furo[3,2-*b*]indoles and propargyl esters. The cascade sequence involves initial formation of a gold-carbene specie via cationic gold(I) catalysed 1,2-acyloxy migration of properly substituted propargyl esters followed by gold-carbene to furoindole addition and successive furan ring-opening affording the final products. The obtained compounds contain an extended π-system linked at the C2 of the indolin-3-ones, they are characterised by intense colouration (from yellow to purple) and were characterised by UV mesearurements.

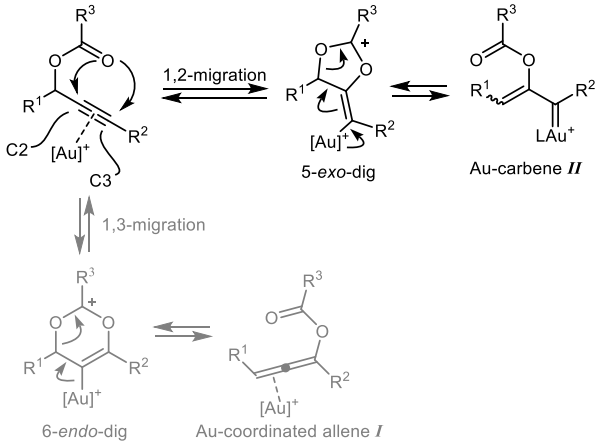
Introduction

Homogeneous gold catalysis has established for long time as a powerful tool in synthetic organic chemistry.[1] Inter alia, the richness of developed chemistry is related to the ability of gold species to activate π-systems under extremely mild conditions with tuneable selectivity allowing for the construction of highly substituted and fascinating complex structures.[2] In particular, homogeneous gold-catalysed *cascade* processes have been widely employed for the effective synthesis of complex heterocycles and natural products.[3] In connection with our recent studies on the gold catalysed reactions of indoles,[4] we recently published our results on the gold-catalysed cascade rearrangement of 2-methyl-4*H*-furo[3,2-*b*]indoles to indolin-3-one derivatives in the presence of gold-activated allenamides ***I*** (Scheme 1a).[5] The reaction occurred through a cascade sequence involving addition of a gold-activated allene to the C2 furan moiety of the starting furoindole followed by a ring-opening/ring-closing event affording 2-spirocyclopentane-1,2-dihydro-3*H*-indolin-3-ones. In a related perspective, Echavarren and co-workers reported the reactions of furans with gold(I)-carbenes ***II*** generated in situ from propargyl esters, 1,6-enynes and 7-substituted-1,3,5-heptatrienes (Scheme 1b).[6] The reactions occur through a mechanism initiated by the electrophilic addition of gold(I)-carbenes to furans followed by furan ring opening. These results led us to explore the chance to involve the C2-C3 bond of C2 unsubstituted furoindoles in a gold(I) catalysed cascade reaction with gold(I)-carbene complexes ***II*** generated in situ from suitable propargyl esters via gold-catalysed 1,2-acyloxy migration (Scheme 1c). The obtained results demonstrated that the reaction proceeds via gold-carbene addition to furoindole followed by furan ring-opening reaction giving rise to 2-alkenyliden-indolin-3-ones.



Scheme 1 Previous and proposed work.

Propargyl esters are useful substrates for cascade reactions given their ability to generate, via gold-catalysed 1,2-or 1,3-acyloxy migration, gold-coordinated allenes ***I*** and gold-carbenes ***II*** able to participate in cascade processes (Scheme 2).[7]

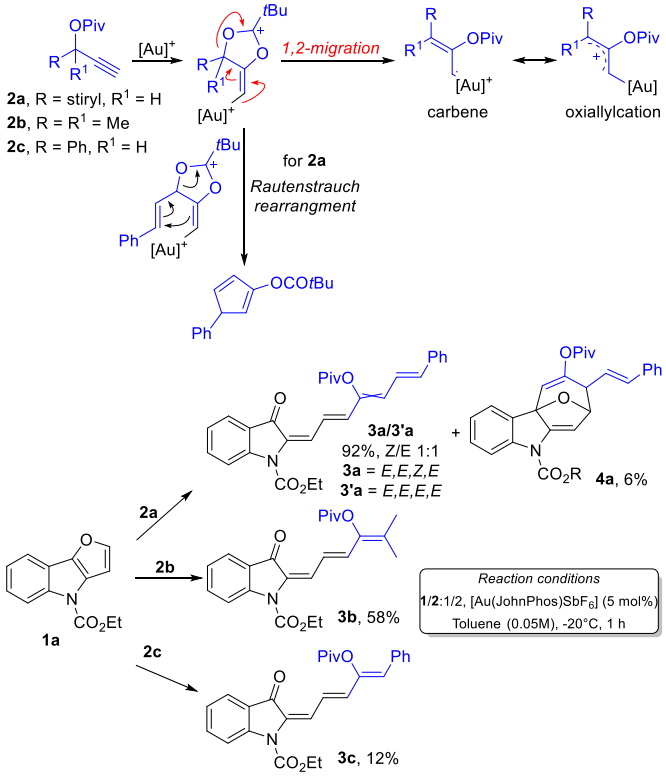


Scheme 2 Propargyl esters, general reactivity patterns.

Moreover, these structurally varied intermediates demonstrated to be in equilibrium with each other and, as a general rule, 1,3-migration is favoured for internal alkynes whereas 1,2-migration prevails for terminal alkynes and EWD-substituted alkynes. Herein, we disclose the full details of our investigations.

Results and discussion

We reported in detail the synthesis of the 4*H*-furo[3,2-*b*]indoles employed in this work in a recently published paper.[5] As a proof of concept, we tested the reactivity of furoindole **1a** with propargyl esters **2a-c** bearing different substituents at the α-position (Scheme 3) and able to furnish, in the presence of gold(I) catalysts, the corresponding carbene-oxiallylcation species.[8] In addition, the reaction outcome could be complicated with propargyl ester **2a** by the formation of the Rautenstrauch rearrangement product (Scheme 3a).[7,9] We performed the planned model reactions in toluene at -20 °C, in the presence of two equivalents of **2a-c** and of 5 mol% of preformed cationic JohnPhosAuSbF$_6$ catalyst. With propargyl ester **2a** the reaction resulted in the isolation in excellent yield of a separable 1:1 mixture of *Z*/*E* isomeric 2-(hepta-2,4,6-trien-1-ylidene)-3-oxoindolines **3a** and **3'a** beside a small amount of tetracyclic compounds **4a**. Analytical (MS) and spectral data (1D and 2D NMR) confirmed the structures of all isolated compounds. Inter alia, the geometries around the double bonds of the heptatrienyl moieties were determined by 2D NOESY NMR spectroscopy and by ^3J Z/E coupling constant analysis. Analysis of 2D COSY, TOCSY, HSQC and NOESY spectra determined the regiochemistry of compound **4a**. With propargyl ester **2b** the reaction afforded in moderate yield 2-((*E*)-5-methyl-hexa-2,4-dien-1-ylidene)-3-oxoindoline **3b**.



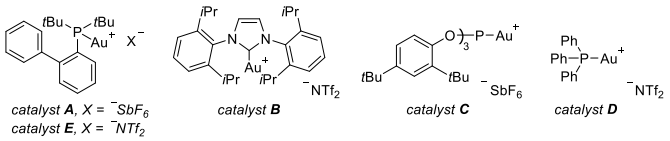
Scheme 3 Preliminary results.

The structure was assigned as reported above for compounds **3a** and **3'a**. It is worth to underline that at the end of the reaction, after the usual work-up, the ^{1}H NMR analysis of the crude revealed the presence of two *Z/E* isomers. However, after the chromatographic purification step, a total conversion towards the **3b** was observed. Finally, with propargyl ester **2c** the reaction resulted in the isolation in poor yield of 2-((2*E*,4*Z*)-5-phenyl-penta-2,4-dien-1-ylidene)-3-oxoindoline **3c**. Besides **3c**, starting unreacted furoindole **1a** and some decomposition compounds were detected. With these results in hand, we decided to explore in detail the reactivity of α-stiryl substituted propargyl esters by evaluating the influence on the reaction outcome of different gold(I) ligands, counterions, solvents and stoichiometry, table 1. As a model reaction, we choose the reaction between **1a** and **2a** (Scheme 3 and Table 1, entry1).

Table 1 Optimization of reaction conditions[a]

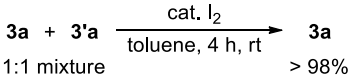
Entry	Au(I)[b]	Solvent	**2a**	Temp. (°C)	Time (h)	**3a** (%)[c]	**3'a** (%)[c]	**4a** (%)[c]
1	A	Toluene	2	-20	1	45	47	6
2[d]	B	Toluene	2	-20	43	15	6	6%
3	C	Toluene	2	-20	1	36	12	28%
4[d]	D	Toluene	2	-20	1	25	/	21%
5	E	Toluene	2	-20	1	40	41	7%
6	A	TFE	2	-20	1	38	43	/
7	A	DCM	2	-20	1	47	46	4
8	**A**	**Toluene**	**1.2**	**-20**	**1**	**58**	**36**	**6%**
9	A	Toluene	1.2	-35	10	/	/	/
10	A	Toluene	1.2	rt	1	14	6	/

[a] All reactions were carried out using **1a** (0.2 mmol) and **2a** (0.24-0.4 mmol, manual dropwise addition) in the stated solvent (0.05 M). [b] 5 mol%, preformed catalysts. [c] Isolated yield. [d] Some decomposition products were observed beside starting **1a**.



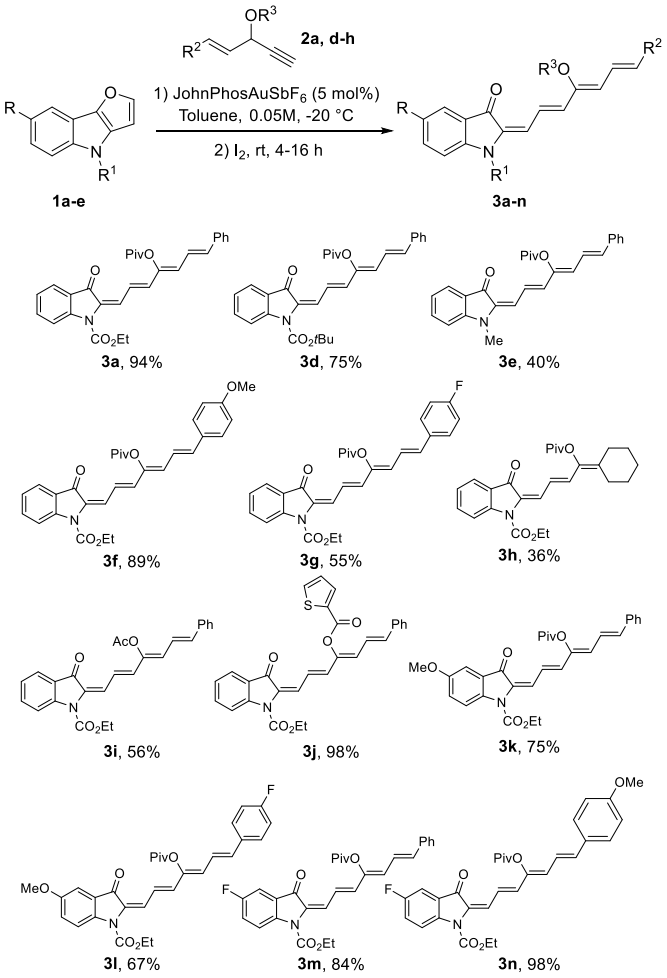
The use of a less electrophilic catalyst[2a] such as cationic gold(I) carbene complex **B** gave poorer results and starting **1a** was recovered after prolonged reaction time beside small amounts of the desired compounds and some decomposition products, table 1, entry 2. The use of more electrophilic cationic gold(I) phosphite **C** or triphenylphosphine **D** complexes resulted in better yields but poorer selectivity with respect to the model reaction, table 1, entries 3 and 4. Then we returned to JohnPhos ligand changing the counterion from SbF_6 to NTf_2 with practical no effect on the reaction outcome, table 1, entry 5. The same was observed when trifluoroethanol or dichloromethane were used as solvents, table 1, entries 6 and 7. However, toluene is less expensive than TFE and dissolves the reaction products better than DCM, so toluene was chosen as the best reaction medium. Moreover, reduction of the equivalents of **2a** to 1.2 did not affect the reaction outcome, table 1 entry 8. In the last two trials, we checked the influence of the temperature on the reaction outcome, table 1, entries 9 and 10. Whereas no reaction occurred lowering the temperature to -35 °C, at 20 °C the reaction resulted in the isolation of **3a** and **3'a** in poor yields beside a series of tarry and unidentified compounds. It is worth to note that the analysis of the crude reaction mixture did not allow revealing the presence of the Rautenstrauch rearrangement product (see Scheme 3).[9] In our opinion, this means that, starting from gold activated propargyl ester **2a**, the 1,2-migration and the subsequent carbene addition to furoindole **1a** are faster than the Rautenstrauch rearrangement process even at room temperature. As a proof of concept, the reaction was repeated in the absence of **1a** and resulted in the isolation of the [4+3] cycloadduct between the Rautenstrauch rearrangement product and propargyl ester **2a**[9b] (see Supporting Information). At this stage of our work, screening for the search of the best reaction conditions for the synthesis of **4a** were not subjected to in deep investigations. The results of this screening allowed for the establishment of the conditions reported in table 1 entry 8 as the best reaction conditions for the synthesis of **3a** and **3'a**.

Then, we explored the possibility to obtain the 3-oxo-2-(hepta-2,4,6-trien-1-ylidene)indolines **3**/**3'** as single isomers. This was done by quenching the reaction with 15 mol% of triphenylphosphine and then treating the solution with a catalytic amount of iodine. The conversion of a mixture of **3a**/**3'a** isomers to **3a** isomer was successful completed (> 98%) in 4 hours (Scheme 4).



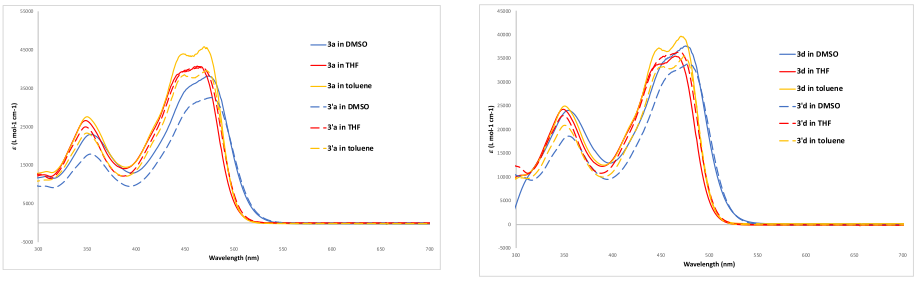
Scheme 4 Isomerization of a **3a**/**3'a** mixture to pure **3a**.

Starting from these results, we then explored the scope of the reaction performing all experiments as reported in the footnote of table 1 under the reaction conditions shown in table 1, entry 8. At the end, the reaction mixtures were quenched with triphenylphosphine and then treated with iodine. Compounds **3a-n** were isolated and characterized after chromatographic purification (Scheme 5).



Scheme 5 Reaction scope.

We firstly performed the reaction between **1a** and **2a** obtaining **3a** as single isomer with excellent yield. Then, we investigated the influence of the protecting group at the nitrogen position on the yield. In particular, we observed that a bulkier electron-withdrawing group such as *N*-Boc led to the formation of the corresponding product **3d** in lower yield. In addition, the substitution of the starting furoindole with an electron-donating N-methyl group was poorly tolerated and the yield in the formation of **3e** significantly decreased down to 40%. Next, we observed that the substitution pattern of the starting propargyl ester **2a, d-h** had a strong impact on the reaction outcome. The introduction on the styryl ring of an electron-donating methoxy group, in fact, gave excellent results both with standard furoindole **1a** and 7-fluorine-substituted furoindole **1e** (respectively **3f** 89% and **3n** 98%). On the contrary, the presence an electron-withdrawing group negatively influenced the formation of compounds **3g** and **3l**, which were isolated in lower 55% and 67% yields, respectively. As shown previously (Scheme 3) disubstituted propargyl ester reacted less efficiently and the corresponding product **3h** was obtained in poorer 36% yield. The modification of the OR^3 group in the ester led to remarkable results. Moving from pivalate to less hindered acetate compound **3i** was isolated in 56% yield, while the use of a more electron-withdrawing thienyl derivative afforded **3j** in high 98% yield. Finally, we focused our attention on the modification of the indole core of **1a-g** and we noticed that the introduction of substituents having different electronic properties at the C7 was well tolerated. In particular, methoxy-substituted indoles provided **3k** and **3l** with a slightly diminished but still good 75% and 67% yields, respectively. Instead, fluorine-substituted products **3m** and **3n** were synthetized with excellent 84% and 98% yields starting from the corresponding fluorinated indole **1e**. In most of cases, the corresponding tetracyclic compounds **4** were detected in traces in the crude reaction mixtures via ^{1}H NMR. Moreover, for the highly conjugated compounds **3** a preliminary set of photophysical properties were collected. In particular, we choose compounds **3a**/**3'a** (isolated during the preliminary reactivity tests) and **3d**/**3'd** (isolated performing the standard reaction avoiding the iodine mediated isomerization step). We measured the UV/Vis spectra for these compounds, in three different solvents with increasing polarity: toluene, THF and DMSO. From the absorbance values we obtained the molar extinction coefficient using the linear regression method (See supporting information for details). The spectra show two peaks at about 350 and 470 nm (Figure 1).



a) **b)**

Figure 1 a) Extinction coefficient of both 3a (bold lines) and 3'a (dotted lines) and b) extinction coefficient of both 3d (bold lines) and 3'd (dotted lines) measured in solvents of different polarity (DMSO in blue, THF in red and toluene in yellow)

For both isomers of compounds **3a** and **3d**, absorption wavelengths are essentially the same. The main difference between the *Z/E* spectra is the value of absorbance (and therefore extinction coefficient). As shown in table 2, molar extinction coefficient values for both *Z* compounds are greater than those for *E* isomers, the only exception being the more red shifted peak of 3d in THF. The solvatochromism is rather small for all derivatives. More than the absorption wavelength, different solvents cause an extinction variation. In particular, the larger extinction coefficient variations are observed in derivative 3'a, when switching from DMSO to THF.

Table 2 Extinction coefficient for **3a**/**3'a** and **3d**/**3'd** measured in solvents of different polarity

	DMSO		THF		Toluene	
Compound	ε (L mol^{-1} cm^{-1})		ε (L mol^{-1} cm^{-1})		ε (L mol^{-1} cm^{-1})	
3'a	ε_{353} 17873	ε_{474} 32504	ε_{348} 24985	ε_{468} 40446	ε_{349} 23324	ε_{472} 39580
3a	ε_{354} 22988	ε_{474} 38170	ε_{348} 26630	ε_{466} 40636	ε_{350} 27593	ε_{470} 45751
3'd	ε_{355} 18604	ε_{479} 33831	ε_{349} 22986	ε_{466} 36935	ε_{350} 20826	ε_{474} 35413
3d	ε_{354} 24052	ε_{476} 37628	ε_{349} 24209	ε_{465} 35417	ε_{351} 24945	ε_{471} 39690

The photoisomerization reaction was followed by UV irradiating pure **3'd** and **3'a** solution in DMSO ($2x10^{-5}$ M) with a 200 W lamp until complete conversion to the *Z* isomer was observed. The photoisomerization was carried out in a rotaflo-equipped cuvette in order to avoid solvent evaporation during the conversion and thus keep a constant concentration of the species in solution. Measurements have been taken every 20 minutes to monitor the isomerization from *E* to *Z* and, as expected, an increasing of the extinction coefficient is observed. In both cases, the equilibrium is reached in nearly 2h, as determined by plotting the intensity of peak at 354 nm vs time (Figure 2). Upon prolonged times (6h), slight decomposition of the products is observed (see Supporting Information).

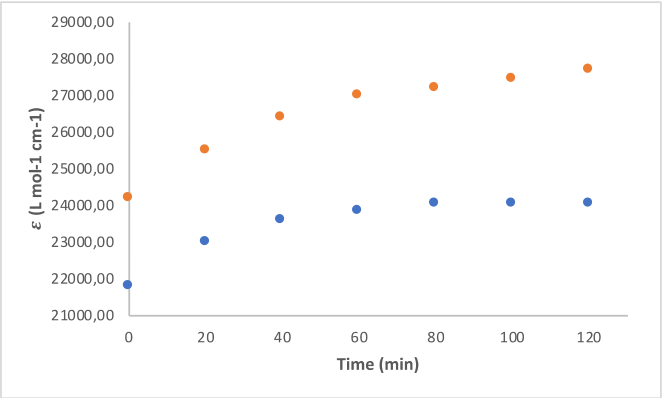
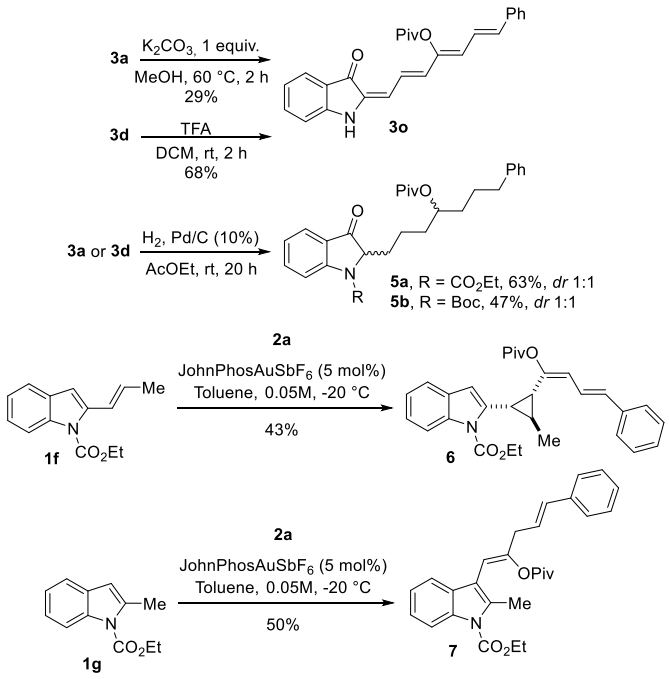


Figure 2 Extinction coefficient *vs* time at 354 nm for 3a (blue) and 3d (orange) measured in DMSO at a concentration of $2x10^{-5}$ M

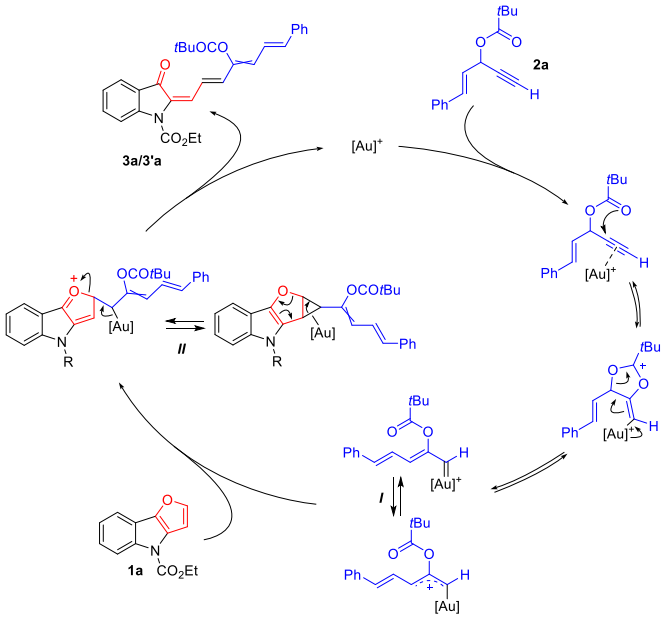
Finally, some simple transformations were realised using compounds 3a and 3d as substrates and two indoles (1f and 1g), different from standard furoindoles, were submitted to the standard reaction conditions (scheme 6).



Scheme 6 Synthetic elaboration of compounds 3 and reactivity of indoles.

We realised the deprotection of both the *N*-CO_2Et and *N*-Boc protected compounds **3a** and **3d** under basic and acidic conditions, respectively. The corresponding 2-alkylydene-3-oxoindole **3o** was isolated in moderate to good yields. Then, we reduced under catalytic conditions the same compounds **3a** and **3d**. Hydrogenation of the entire trienylidene moiety was observed and compounds **5a** and **5b** were isolated as 1:1 mixture of diastereoisomers. Finally, the reactions of 2-vinyl and 2-methyl indoles **1f** and **1g** with **2a** under standard reaction conditions resulted in the isolation of the cyclopropanation adduct (**6**) at the exocyclic double bond of **1f** and of the simple hydroarylation product (**7**) with **1g**. The geometry around the cyclopropane moiety and diene system of **6** were tentatively assigned via 1D and 2D NMR spectroscopy (See supporting information).

Moreover, a mechanism could be easily underlined looking at the literature on both the reactivity of gold carbene complexes[10] and on the electrophiles driven furan ring opening reactions (Scheme 7).[6,11] Activation of the terminal propargyl ester by means of cationic gold(I) catalyst triggers the reversible[12] 1,2-acyloxy migration leading to derivative ***I***. This intermediate can be described as a gold-carbene or as an oxiallyl cation. Therefore, ***I*** reacts as a pure electrophilic carbene with the C2-C3 furan carbons of **1a** to give the corresponding cyclopropanated species ***II*** or, looking at intermediate ***I*** as an oxiallyl cationic specie, intermediate ***II*** could arise from the electrophilic attack to the C2 carbon atom of furoindole **1a**. Finally, both arrangements of intermediate ***II*** evolve *via* furan ring-opening reaction giving rise to the final products **3a/3'a** and restoring the gold(I) catalyst. Probably, the *E/Z* geometry around position 4 at the trienylidene moiyety of **3a/3'a** is a consequence of the dual nature of intermediate ***I*** which possesses a fixed geometry merely in the carbenic form with a geometry dictated by the mechanism of 1,2-migration.



Scheme 7 Proposed reaction mechanism.

Conclusions

An efficient and high yielding methodology for the synthesis of polyconjugated 2-alkylidene-3-oxoindoles was developed. The reaction takes advantage from the ability of cationic gold(I) catalysts to selectively promote the formation of gold-carbenes from propargyl esters under extremely mild reaction conditions. Moreover, apart from the well-known migration step, the gold catalyst is involved also in the electrophilic addition/ring opening sequence with furoindoles demonstrating once again the usefulness of these catalysts in promoting complex cascade reactions. The obtained results represent a clear improvement and expansion of the synthetic concept reported in our previous researches[5] on the electrophiles-driven ring-opening reactions of furoindoles for the synthesis of 3-oxo-indole derivatives. The synthesised compounds represent a new class of 2-alkylyden-3-oxoindoles. Thus, whereas literature references are available for simple 2-methyleneindolin-3-one[13] (indigo derivatives) and 2-allylideneindolin-3-one,[14] to the best of our knowledge literature references for trienylidene derivatives are outdated and scarce.[15]

Experimental

General procedure for the synthesis of 3a-n

To a N_2-flushed solution of 4*H*-furo[3,2-*b*]indole **1** (1 equiv.) and [Au(JohnPhos)SbF_6] (5 mol%) in anhydrous toluene, a solution of propargylic ester **2** (1.2 or 2 equiv.) in toluene (0.5 M) was added dropwise at -20° C. The reaction mixture was stirred for the stated time at -20° C and then quenched with PPh_3 (15 mol%). Then the reaction mixture was warmed to room temperature and further stirred for 4 h in the presence of one crystal of I_2. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography to yield the desired product **3**.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 A. S. K. Hashmi and F. D. Toste, Modern Gold Catalyzed Synthesis; Wiley VCH, Weinheim, 2012.
2 (a) Y.-C. Lee, K. Kumar and H. Waldmann, *Angew. Chem. Int. Ed.*, **2018**, *57*, 5212; (b) J. L. Mascareñas, I. Varela and F. López, *Acc. Chem. Res*., DOI: 10.1021/acs.accounts.8b00567; (c) A. M. Asiri and A. S. K. Hashmi, *Chem. Soc. Rev*., **2016**, *45*, 4471; (d) B. Wagner, K. Belger, S. Minkler, V. Belting and N. Krause, *Pure Appl. Chem*., **2016**, *88*, 391; (e) A. Collado, A. Gomez-Suarez and S. P. Nolan, in Sustainable Catalysis: With Non-endangered Metals, Part 2, RSC Green Chemistry Series 39, ed. M. North, (RSC) Publishing - Royal Society of Chemistry, London, 2016, 16, 41; (f) A. M. Asiria and A. S. K. Hashmi, *Chem. Soc. Rev*. **2016**, *45*, 4471; (g) W. Debrouwer, T. S. A. Heugebaert, B. I. Roman and C. V. Stevens, *Adv. Synth. Catal*. **2015**, *357*, 2975; (h) R. Dorel and A. M. Echavarren, *Chem.*

Rev. **2015**, *115*, 9028; (i) D.-H. Zhang, X.-Y. Tang and M. Shi, *Acc. Chem. Res*., **2014**, *47*, 913; (j) W. Yang and A. S. K. Hashmi, *Chem. Soc. Rev*., **2014**, *43*, 2941; (k) A. Furstner, *Acc. Chem. Res*. **2014**, *47*, 925.

3 (a) W. Fang and M. Shi, *Chem. - Eur. J.,* **2018**, *24*, 9998; (b) A. Furstner, *Angew. Chem., Int. Ed*., **2018**, *57*, 4215; (c) R. Quach, D. P. Furkert and M. A. Brimble, *Org. Biomol. Chem*., **2017**, *15*, 3098; (d) Q. Wang and M. Shi, Min, *Synlett* **2017**, *28*, 2230; (e) F. Pan, C. Shu and L.-W. Ye, *Org. Biomol. Chem*., **2016**, *14*, 9456; (f) A. Blanc, V. Beneteau, J.-M., Weibel and P. Pale, *Org. Biomol. Chem*., **2016**, *14*, 9184; (g) B. Wagner, K. Belger, S. Minkler, V Belting and N. Krause *Pure App. Chem*., **2016**, *88*, 391; (h) Y. Wang and L. Zhang, in Catalytic Cascade Reactions, Ed. P.-F. Xu and W. Wang, John Wiley and Sons, Hoboken, 2014, 4, 145; (i) Y. Zhang, T. Luo and Z. Yang, *Nat. Prod. Rep*., **2014**, *31*, 489.

4 Reviews: (a) E. Rossi, G. Abbiati and V. Pirovano, *Eur. J. Org. Chem*., **2017**, *31*, 4512; (b) V. Pirovano, *Eur. J. Org. Chem*., **2018**, *17*, 1925; selected recent papers: (c) V. Pirovano, M. Borri, G. Abbiati, S. Rizzato and E. Rossi, *Adv. Synth. Catal.*, **2017**, *359*, 1912; (d) V. Pirovano, M. Negrato, G. Abbiati, M. Dell'Acqua and E. Rossi, *Org. Lett.*, **2016**, *18*, 4798; (e) E. Rossi, G. Abbiati, M. Dell'Acqua, M. Negrato, A. Paganoni and V. Pirovano, *Org. Biomol. Chem.*, **2016**, *14*, 6095; (f) V. Pirovano, E. Arpini, M. Dell'Acqua, R. Vicente, G. Abbiati and E. Rossi, *Adv. Synth. Catal.*, **2016**, *358*, 403.

5 V. Pirovano, E. Brambilla, S. Rizzato, G. Abbiati, M. Bozzi and E. Rossi, *J. Org. Chem*., **2019**, *84*, 5150.

6 D. Leboeuf, M. Gaydou, Y. Wanga and A. M. Echavarren, *Org. Chem. Front*., **2014**, *1*, 759.

7 (a) Ref.1, pag. 75-134; (b) S. Wang, *Tetrahedron Lett.*, **2018**, *59*, 1317; (c) D. P. Day and P. W. H. Chan R., *Adv. Synth. Catal.*, **2016**, *358*, 1368; (d) B. J. Ayers and P. W. H. Chan, *Synlett*, **2015**, *26*, 1305; (e) Kazem Shiroodi and V. Gevorgyan, *Chem. Soc. Rev.*, **2013**, *42*, 4991.

8 For a discussion on the nature of gold-carbenes see: (a) C. García-Morales, X.-L. Pei, J. M. Sarria Toro and A. M. Echavarren, *Angew. Chem. Int. Ed*., **2019**, *58*, 3957; (b) R. J. Harris and R. A. Widenhoefer, *Chem. Soc. Rev*., **2016**, *45*, 4533; (c) Y. Wang, M. E. Muratore and A. M. Echavarren, *Chem. Eur. J.*, **2015**, *21*, 7332.

9 (a) X. Shi, D. J. Gorin and F. D. Toste, *J. Am. Chem. Soc.*, **2005**, *127*, 5802; (b) J. Zhao, S. Yang, X. Xie, X. Li and Y. Liu, *J. Org. Chem.*, **2018**, *83*, 1287; (c) M. Mathiew, J. K. Tan and P. W. H. Chan, *Angew. Chem. Int. Ed.*, **2018**, *57*, 14235; (d) X. Chen, D. P. Day, W. T. Teo and P. W. H. Chan, *Org. Lett.*, **2016**, *18*, 5936; (e) C. Bürki, A. Whyte, S. Arndt, A. S. K. Hashmi and M. Lautens, *Org. Lett.*, **2016**, *18*, 5058; (f) D. Susanti, L.-J. Liu, W. Rao, S. Lin, D.-L. Ma, C.-H. Leung and P. W. H. Chan, *Chem. Eur. J.*, **2015**, *21*, 9111.

10 (a) D. Qian and J. Zhang, *Chem. Soc. Rev*., **2015**, *44*, 677; (b) S. Shin, *Top. Curr. Chem*., **2015**, *357*, 25.

11 Reviews: (a) A. V. Butin, V. T. Abaev, T. A. Stroganova and A. V. Gutnov, in Targets in Heterocyclic Systems,Ed. O. A. Attanasi and D. Spinelli, Societa Chimica Italiana, Roma, 2001, *5*, 131; (b) I. V. Trushkov, M. G. Uchuskin and A. V. Butin, *Eur. J. Org. Chem*., **2015**, 2999; selected papers: (c) L. El Kaim, L. Grimaud and S. Wagschal, *Chem. Commun*., **2011**, *47*, 1887; (d) B. Yin, H. Yu, Z. Li, W. Zhong and W. Gu, *Synthesis*, **2012**, *44*, 3735; (e) A. V. Butin, M. G. Uchuskin, A. S. Pilipenko, F. A. Tsiunchik, D. A. Cheshkov and I. V. Trushkov, *Eur. J. Org. Chem*., **2010**, 920; (f) V. T. Abaev, A. T. Plieva, P. N. Chalikidi, M. G. Uchuskin, I. V. Trushkov and A. V. Butin, *Org. Lett*., **2014**, *16*, 4150; (g) B. Yin, C. Cai, G. Zeng, R. Zhang, X. Li, and H. Jiang, *Org. Lett*., **2012**, *14*, 1098; (h) S. Muthusamy and D. Azhagan, *Tetrahedron Lett*., **2011**, *52*, 6732; (i) A. J. S. Alves, S. M. M. Lopes, M. S. C. Henriques, J. A. Paixão and T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem*., **2017**, 4011; (j) S. M. M. Lopes, M. S. C. Henriques, J. A. Paixão and T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem*., **2015**, 6146; (k) Y. Chen, G. Li and Y. Liua, *Adv. Synth. Catal*., **2011**, *353*, 392.

12 W. Rao, Sally, S. N. Berry and P. W. H. Chan, *Chem. Eur. J.*, **2014**, *20*, 13174.

13 C. Petermayer, S. Thumser, F. Kink, P. Mayer, and H. Dube, *J. Am. Chem. Soc*., **2017**, *139*, 15060 and references cited therein.

14 (a) A. D. Dubonosov, L. M. Sitkina, V. A. Bren, A. Y. Bushkov and V. I. Minkin, *Chem Heterocycl Compd*, **1984**, *20*, 951; (b) C. Guo, M. Schedler, C. G. Daniliuc, and F. Glorius, *Angew. Chem. Int. Ed*., **2014**, *53*, 10232.

15 (a) W. Flitsch, R. A. Jones, and M. Hohenhorst, *Tetrahedron Lett.*, **1987**, *28*, 4397; (b) W. Flitsch, and M. Hohenhorst, Liebigs Annalen der Chemie, **1990**, 449.