



# Gold-catalyzed cascade reactions of 4H-furo[3,2-b]indoles with allenamides: synthesis of indolin-3-one derivatives

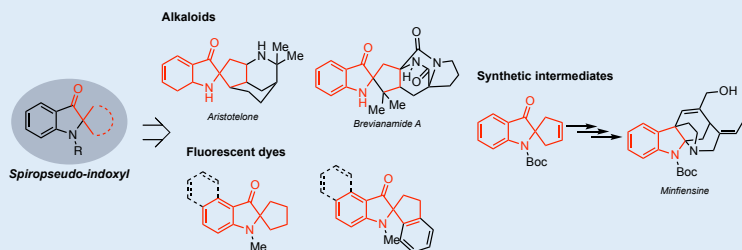
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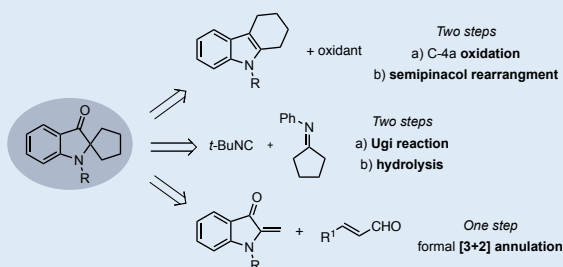


## Introduction

2-Spirocyclopentane-1,2-dihydro-3H-indol-3-ones (namely, **spiropseudo-indoxyls**) represent the core component of biologically relevant alkaloids and of indole-based fluorescent dyes.<sup>1-2</sup> They can also be employed as intermediate in the synthesis of *Minfiensine*.<sup>3</sup>

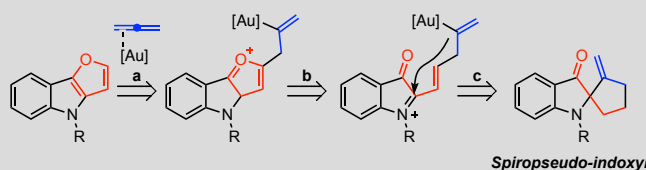


## Reported methods of synthesis:<sup>4-6</sup>



## Our Goal

Synthesis of spiropseudo-indoxyls by gold-catalyzed cascade reaction between 4H-furo[3,2-b]indoles and N-allenamides.

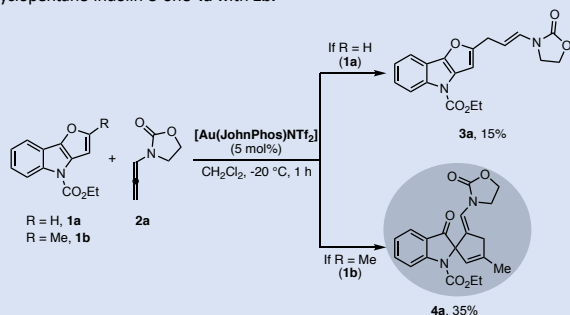


## Planned gold-cascade sequence:

- C-2 hydroarylation of furan ring
- Furan ring opening
- Intramolecular spirocyclization

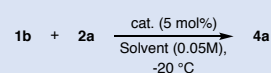
## Initial findings and screening of reaction conditions

Furoindoles **1a** and **1b** were chosen as model compounds for the reactions with allenamide **2a** in the presence of preformed cationic complex  $[Au(JohnPhos)NTf_2]$ . The reactions resulted in the isolation, in low yields, of simple hydroarylation product **3a** with **1a** and of 2-spirocyclopentane-indolin-3-one **4a** with **1b**.



**3a** was isolated in 90% yield using  $[(ArO)_3PAuNTf_2]$  in toluene (0.05 M) at -20 °C. Ar = 2,4-di-*t*-butylphenyl.

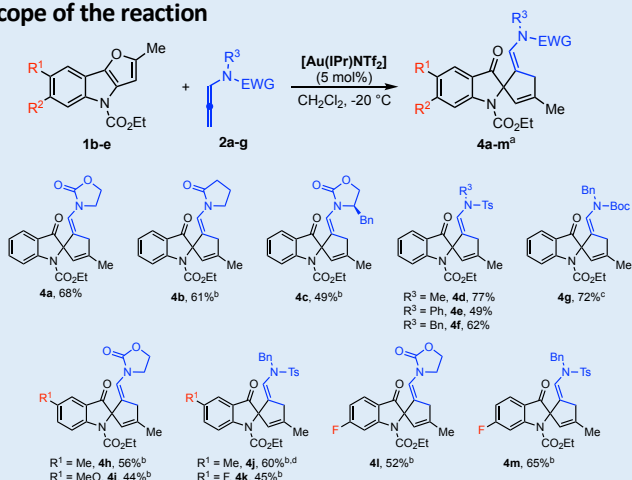
## Optimization of reaction conditions for the synthesis of **4a**



Entry	1b/2a	Catalyst (5 mol %)	Solvent	Time (h)	4a (%) <sup>a</sup>
1	1/2	$[Au(JohnPhos)NTf_2]$	$CH_2Cl_2$	1	35
2	1/1	$[(ArO)_3PAuNTf_2]$	$CH_2Cl_2$	1	32
3	1/1	$[Au(IPr)NTf_2]$	$CH_2Cl_2$	2	57
4	1/1	$[Au(IPr)NTf_2]$	Toluene	2	n.r. <sup>b</sup>
5	1/1.2	$[Au(IPr)NTf_2]$	$CH_2Cl_2$	2	68
6	1/1.2	$[Au(IPr)SbF_6]$	$CH_2Cl_2$	2	63
7	1/1.2	HNTf <sub>2</sub> (20 mol %)	$CH_2Cl_2$	1	n.r. <sup>c</sup>
8	1/1.5	$[Rh(cod)Cl]_2$	$CH_2Cl_2$	24	n.r. <sup>c</sup>
9	1/1.5	$PtCl_2$	$CH_2Cl_2$	24	n.r. <sup>c</sup>

Reaction conditions: **1a** (0.2 mmol) and **2a** (0.2-0.24 mmol, in the stated solvent (0.05 M) at -20 °C. <sup>a</sup> Isolated yields. <sup>b</sup> Complex mixture of products. <sup>c</sup> Unreacted starting materials were recovered. Ar = 2,4-di-*t*-butylphenyl; IPr = chloro[1-(3,5-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)]imidazol-2-ylidene; JohnPhos = (2-biphenyl)-di-*t*-butylphosphine.

## Scope of the reaction

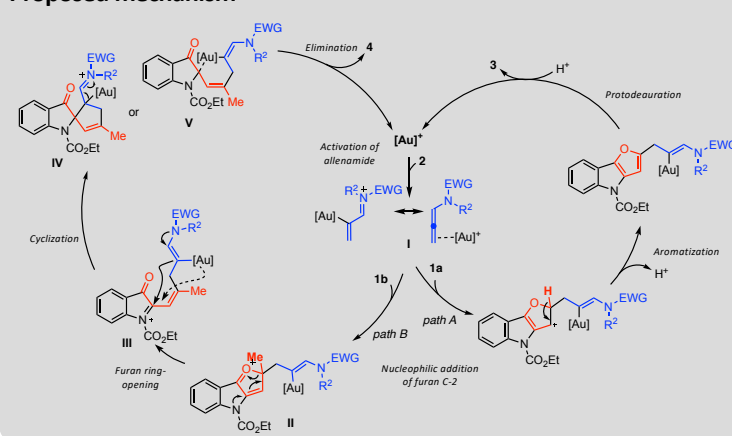


Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol),  $[Au(IPr)NTf_2]$  (5 mol %) in  $CH_2Cl_2$  (0.05 M), -20 °C, 1-18 h. <sup>a</sup> Isolated yields. <sup>b</sup> 1.5 equiv of **2** were used. <sup>c</sup> 2.0 equiv of **2** were used. <sup>d</sup> Slow addition.

## Conclusion<sup>7</sup>

- Design of a novel synthesis of spiropseudo-indoxyl derivatives merging the ability of cationic gold(I) catalysts to activate unsaturated  $\pi$ -systems with the electrophiles driven ring-opening reactions of furans;
- Gold-catalyzed cascade furan C-2 hydroarylation/ring-opening/spirocyclization;
- 13 examples, moderate to high yields;
- Major limitation: necessity to use C-2 substituted furoindoles.

## Proposed mechanism



## References

- Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127.
- Chen, H.; Shang, H.; Liu, Y.; Guo, R.; Lin, W. *Adv. Funct. Mater.* **2016**, *26*, 8128.
- Yu, Y.; Li, G.; Jiang, L.; Zu, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 12627.
- Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1951**, *73*, 2188.
- Schneeckloth, J. S., Jr.; Kim, J.; Sorensen, E. J. *Tetrahedron* **2009**, *65*, 3096.
- Guo, C.; Schedler, M.; Daniliuc, C. G.; Glorius, F. *Angew. Chem. Int. Ed.* **2014**, *53*, 10232.
- Pirovano, V.; Brambilla, E.; Rizzato, S.; Abbiati, G.; Bozzi, M.; Rossi, E. *J. Org. Chem.* **2019**, *84*, 5150.

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