Gold-catalyzed cyclization reaction for the synthesis of biologically relevant polycyclic indole derivatives.

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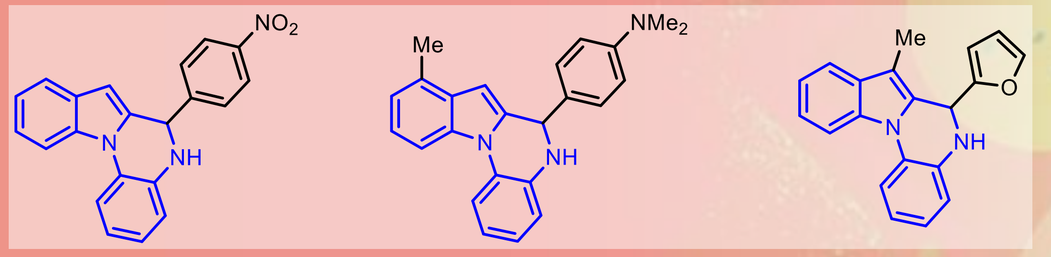
Introduction

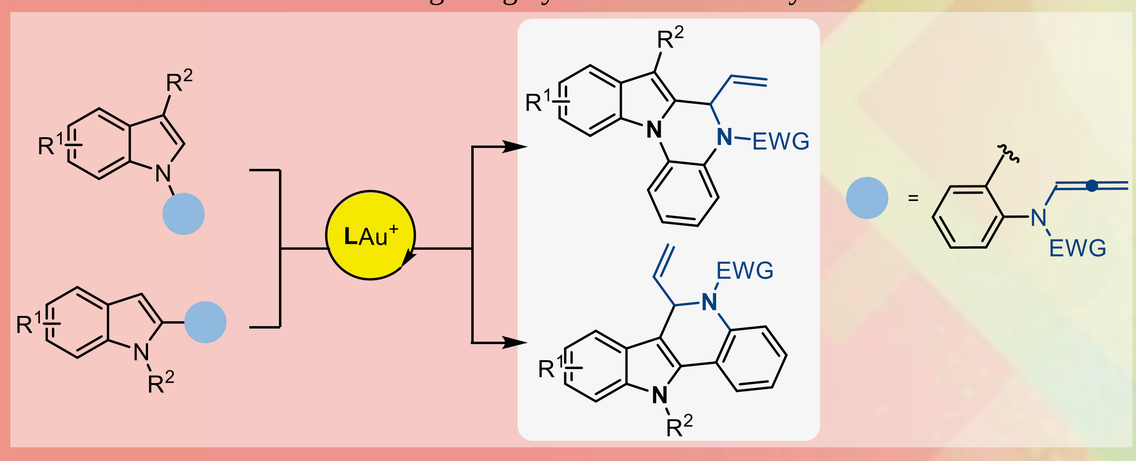
Despite the approval of several antiretroviral agents for clinical use against **HIV**, the efficacy of these treatments remains compromised because of **drug-resistance** and side effects associated with prolonged administration. As a result, there is still a high demand from both society and industry for the discovery and development of novel, selective, and safer compounds for HIV therapy.[1]

In this context, **5,6-dihydroindolo[1,2-*a*]quinoxaline** has emerged as a promising scaffold, demonstrating potent *in-vitro* antiretroviral activity against HIV-infected cells.[2]

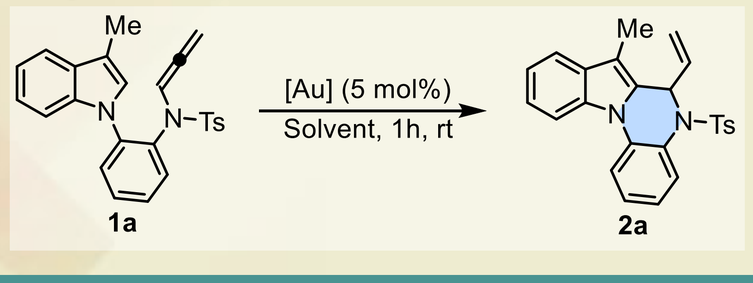


Aim of the work

We have evaluated the possibility of constructing a new class of indolo[1,2-*a*]quinoxalines and 11*H*-indolo[3,2-*c*]quinolines through the cyclization of *N*-allenamides derivatives under **mild and safe catalytic conditions**. This transformation exploits the well-established ability of gold to activate allenic bonds and has as main advantages high yields and selectivity.



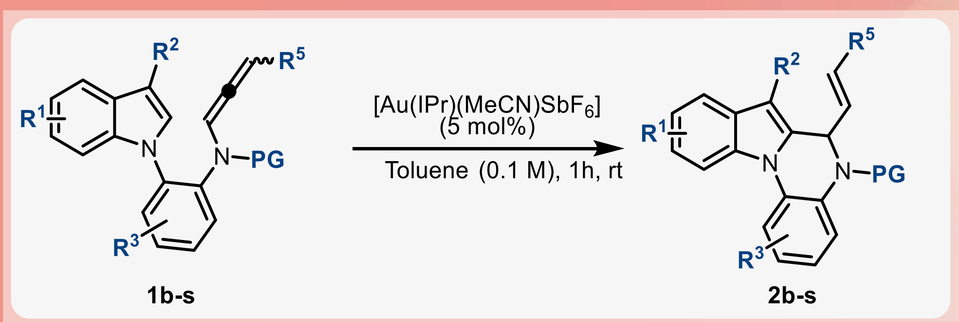
Screening of the reaction conditions

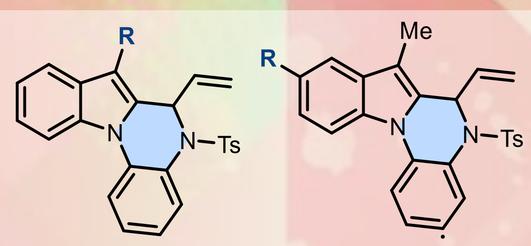


Entry	[Au] (5 mol%)	Solvent (0.1 M)	2a (%)[b]
1	$[Au(IPr)NTf_2]$	CH_2Cl_2	74
2	$[Au(JohnPhos)NTf_2]$	CH_2Cl_2	48
3	$[Au(ArO)_3PNTf_2]$	CH_2Cl_2	52
4	$[Au(PPh_3)NTf_2]$	CH_2Cl_2	23
5	$[Au(IPr)(MeCN)SbF_6]$	CH_2Cl_2	75
6[c]	$[Au(IPr)(MeCN)SbF_6]$	CH_2Cl_2	62
7	$[Au(IPr)(MeCN)SbF_6]$	Toluene	84

[a]Reaction conditions: **1a** (0.1 mmol), [Au] (5 mol%), in anhydrous solvent (1 ml, 0.1 M) at rt for 1 h. [b]Isolated yield. [f]Reaction performed at -20 °C. IPr=1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; JohnPhos=(2-biphenyl)di-*tert*-butylphosphine; Ar=2,4- di-*tert*-butylphenyl.

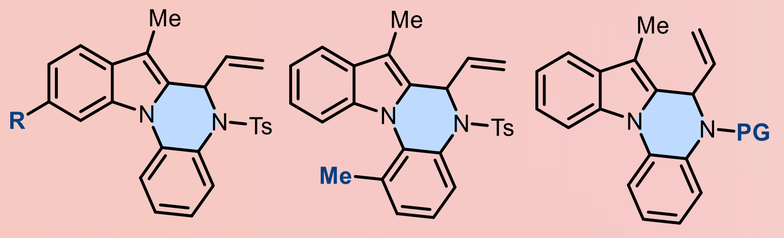
Scope of the reaction





R = Et, **2b**, 99%
R = *i*-Pr, **2c**, 85%
R = Ph, **2d**, 57%
R = 2-Naphthyl, **2e**, 92%

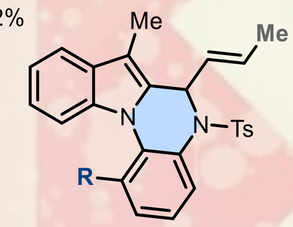
R = Me, **2f**, 78%
R = MeO, **2g**, 79%
R = F, **2h**, 70%



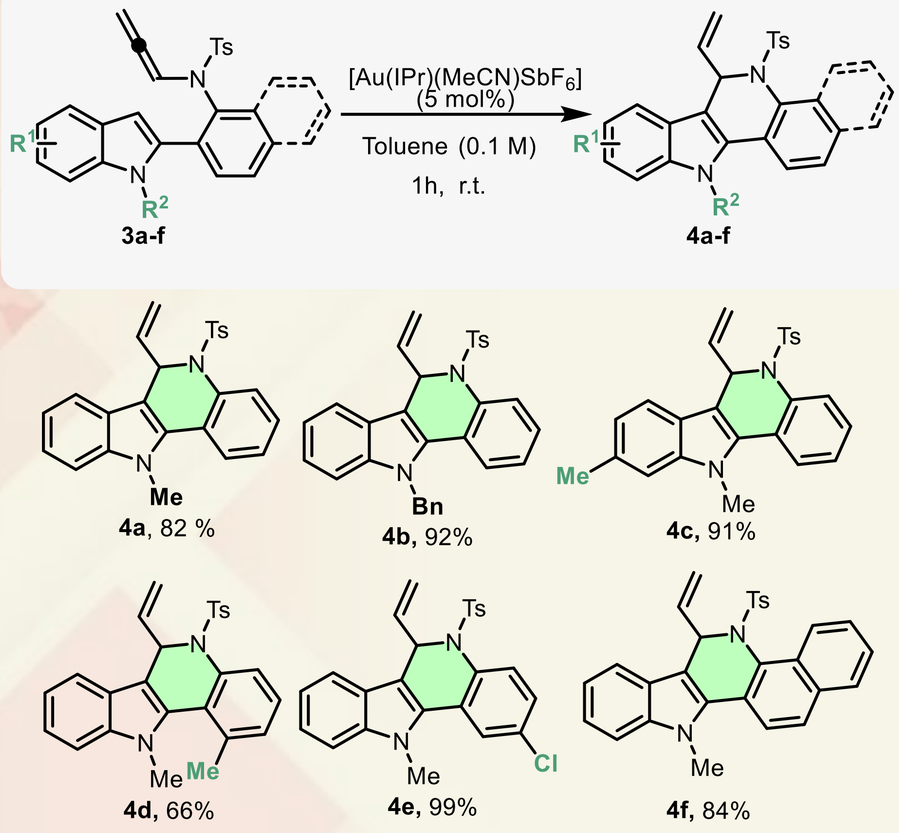
R = Br, **2i**, 72%
R = MeO, **2j**, 93%

2k, 76%

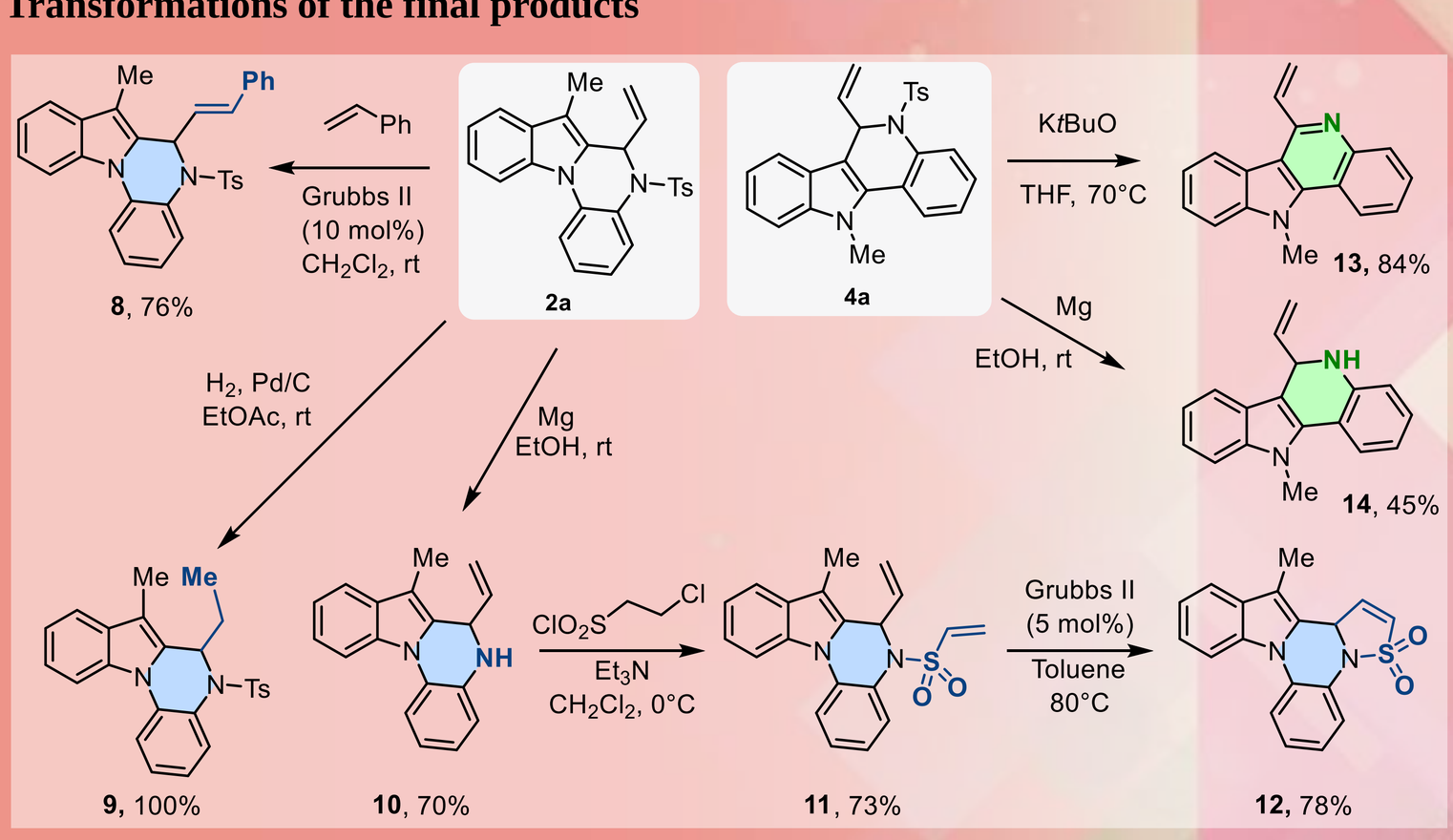
PG= SO_2-2,4,6-$(Me)_3C_6H_2$, **2l**, 99%
PG= SO_2-2,4,6-$(i\text{-}Pr)_3C_6H_2$, **2m**, 99%
PG = SO_2-3,5-$(CF_3)_2C_6H_3$, **2n**, 93%
PG = SO_2-4-NO_2-C_6H_4, **2o**, 89%
PG = SO_2-Me, **2p,** 99%
PG =Cbz, **2q,** 82%



R = H, **2r**, 97%
R= Me, **2s,** 88%



Transformations of the final products



Conclusions

In summary, we have developed a gold-catalyzed cyclization of allenamides[3] that offers effective access to previously uninvestigated indolo[1,2-*a*]quinoxalines and indolo[3,2-*c*]quinolines. The main benefits of our approach are mild reaction conditions and wide substrate scope. The practical utility of the products was further showcased through various post-functionalization transformations, emphasising their potential as versatile building blocks. Given the ubiquitous presence of indole-based polycyclic frameworks in bioactive compounds, we expect that our findings will pave the way for the development of new heteroaromatic architectures.

Acknowledgements

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References

[1] E. Gardner, W. Burman, J. Steiner, P. Anderson, and D. Bangsberg, *AIDS* **2009**, *23*, 1035-1046.
[2] L. Fan, N. Huang, R. Yang, S. He, L. Yang, H. Xu, and Y. Zheng *Lett. Drug Des. Disc.* **2012**, *9*, 44-47.
[3] S. Meraviglia, M. Goudarzi, S. Borsi, G. Abbiati, V. Pirovano, "Gold-Catalysed Cyclization of *N*-Allenamides: synthesis of 5,6-dihydroindolo[1,2-*a*]quinoxalines and 6,11-dihydro-5H-indolo[3,2-*c*]quinolines " submitted to *Org. Biomol. Chem.*