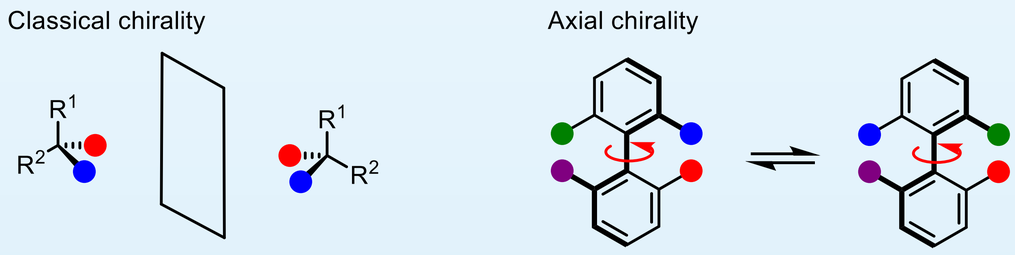
Gold catalyzed asymmetric synthesis of axially chiral indole-fused diazocines.

S. Meraviglia,[a] V. Pirovano,[a] G. Abbiati[a], E. Brambilla[a].

[a]*Dipartimento di Scienze Farmaceutiche, Sezione di Chimica Generale e Organica "A. Marchesini", Via G. Venezian 21, 20133, Milano, Italy;*
e-mail: silvia.meraviglia@unimi.it

Introduction

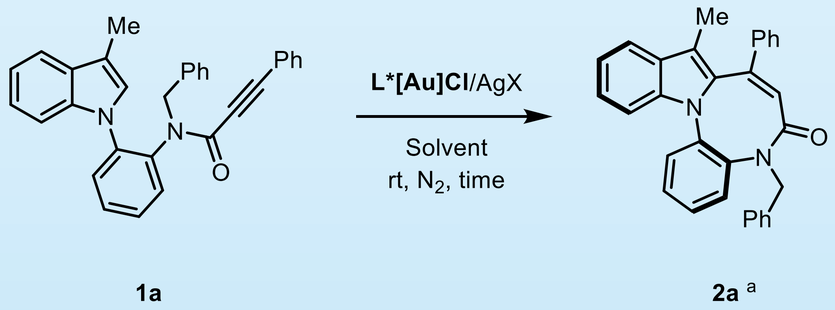
Atropisomerism, also called **axial chirality**, is a particular kind of chirality in which the rotation of a σ bond is constrained because of the steric or electric effects of bulky substituents. This type chirality shows **great potential for drug development** and has been observed in natural products. In addition, **many chiral catalysts and ligands** that are frequently used in asymmetric synthesis are axially chiral compounds.[2]



Objective

Among these substrates, axially chiral indole derivatives have been recognized as **an important class of five-membered heterobiaryls**, because of their presence in some natural alkaloids, chiral phosphine ligands and bioactive molecules.[3] Taking into account these premises, we are now developing a gold catalyzed asymmetric synthesis of axially chiral indole-fused diazocines.

Screening of the reaction conditions

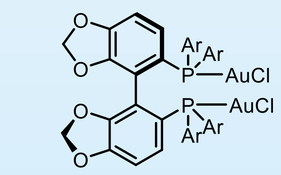


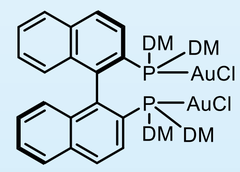
1a **2a** [a]

[a] *Only major enantiomer is represented.*

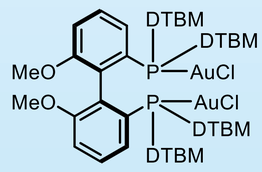
Entry	L*[Au]Cl (5 mol%)	AgX (5 mol%)	Solvent	Time (h)	Yield (%)	e.r.
1	(R)-DTBM-SEGPHOS Au_2Cl_2	$AgSbF_6$	DCM	24	Traces	/
2	(R)-DM-SEGPHOS Au_2Cl_2	$AgSbF_6$	DCM	48	17	30:70
3	(R)-DM-BINAP-Au_2Cl_2	$AgSbF_6$	DCM	48	20	45:55
4	(R)-DTBM-BIPHEP-Au_2Cl_2	$AgSbF_6$	DCM	24	/	/
5	(S,R,R)-SPINOL-AuCl	$AgSbF_6$	DCM	24	82	48:52
6	C1	$AgSbF_6$	DCM	24	75	70:30
7	C2	$AgSbF_6$	DCM	24	99	92:8
8	C3	$AgSbF_6$	DCM	48	71	75:25
9	C4 [b]	$AgSbF_6$	DCM	48	26	72:28
10	C5	$AgSbF_6$	DCM	48	56	65:35
11	C6 [b]	$AgSbF_6$	DCM	48	/	/
12	C2	$AgBF_4$	DCM	29	66	95:5
13	C2	$AgNTf_2$	DCM	29	78	93:7
14	C2	AgTf	DCM	48	41	93:7
15	C2	$AgSbF_6$	Toluene	48	38	98:2
16	C2	$AgBF_4$	Toluene	48	/	/
17	C2	$AgSbF_6$	DCE	24	95	90:10
18	C2	$AgSbF_6$	Cl-Ph	25	94	98:2

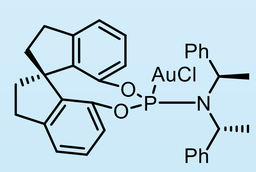
*Reaction conditions: catalyst (5 mol%), AgX (5 mol%), 1 mL solvent, at rt for 10 minuts, then **1a** (0.1 mmol), at rt for 24-48 h.*
[b] *Catalyst was prepared in situ from the corresponding ligand and $(CH_3)_2SAuCl$.*

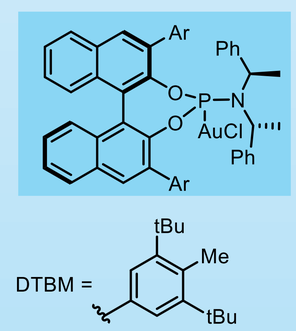

Ar = DTBM
(R)-DTBM-SEGPHOS Au_2Cl_2


(R)-DM-BINAP-Au_2Cl_2

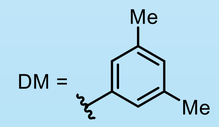
Ar = DM
(R)-DM-SEGPHOS Au_2Cl_2

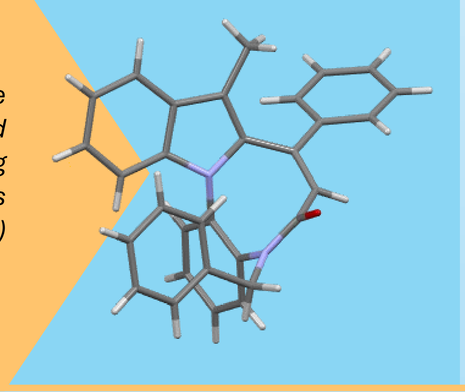

(R)-DTBM-BIPHEP-Au_2Cl_2


(S,R,R)-SPINOL-AuCl


Ar = 2-naphtyl **C1**
Ar = 3,5-CF_3-Ph **C2**
Ar = pyrenyl **C3**
Ar = 2,4,6-triiPr-Ph **C4**
Ar = 1-naphtyl **C5**
Ar = antracenyl **C6**

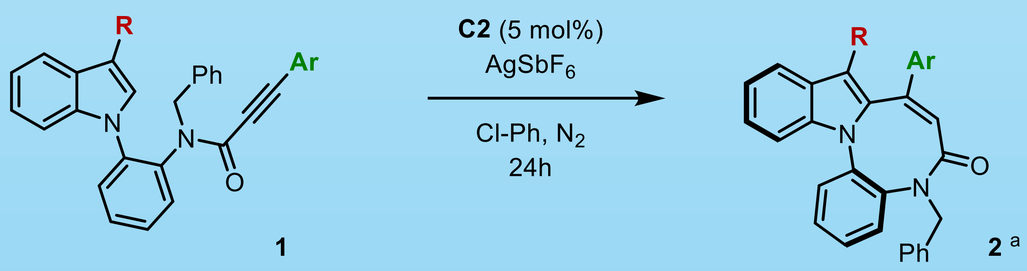
DTBM =


DM =



*The structure of **2a** as pure enantiomer was elucidated by X-Ray analysis confirming the presence of a chiral axis on the indole N–C(aryl) bond.*

Scope of the reaction



1 **2** [a]

Variation on the indole ring

R = Me **2a** 94% e.r. 98:2
R = Et **2b** 81% e.r 96:4
R = Ph **2c** 88% e.r. 92:8

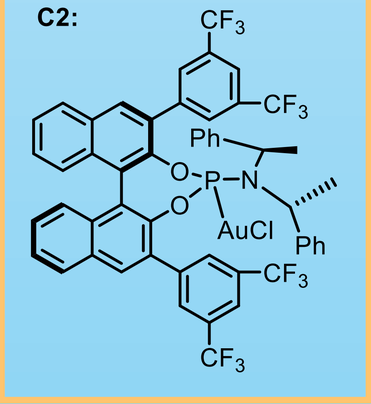
Variation on the aryl ring

Ar = 4-Me-Ph **2d** 72% e.r. 98:2
Ar = 4-MeO-Ph **2e** 86% e.r 98:2
Ar = 4-F-Ph **2f** 76% e.r. 98:2
Ar = 3-Me-Ph **2g** 42% e.r. 97:3
Ar = 2-Napht **2h** 78% e.r. 98:2

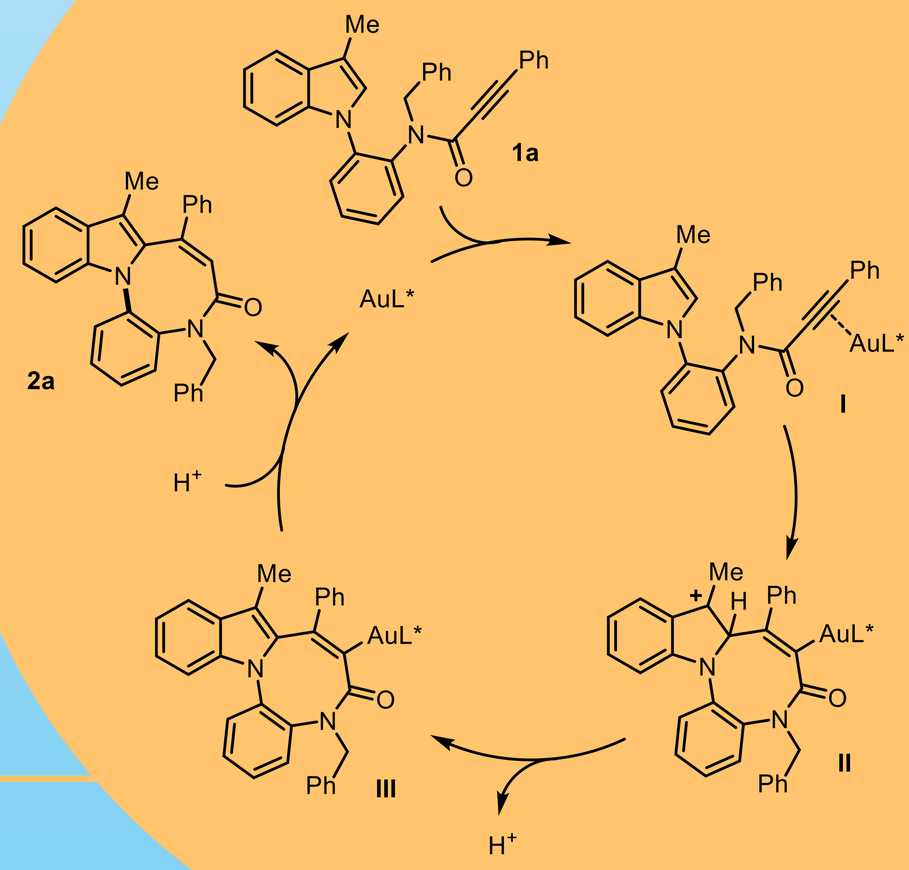
In progress

[a] *Only major enantiomer is represented.*

C2:



Proposed mechanism[4]



Future perspectives

- [x] Optimization of the reaction conditions
- [x] Preliminary scope with different functional groups on the aryl and the indole ring
- [ ] Expansion of the scope with other functional groups and protecting groups for the amidic nitrogen
- [ ] Evaluation of the rotational energy of the chiral axis

References

1. *Org. Chem. Front*. **2022**, *9*, 2280–2292.
2. *J. Med. Chem.* **2011**, *54*, 7005–7022; *J. Med. Chem*. **2022**, *243*, 114700.
3. *Chem. Eur. J.* **2020**, *26*, 15779–15792.
4. *Chem. Comm*. **2012**, *48*, 6550–6552; *Chem. Rev.* **2021**, *121*, 8756–8867.

Acknowledgements

We acknowledge MUR-Italy (PostDoc fellowship to E. Brambilla) for financial support. Prof. S. Rizzato is thanked for X-ray analyses, D. Nava and L. Feni (University of Milan) are thanked for NMR and HPLC analyses. Mass spectrometry analyses were performed at the Mass Spectrometry facility of the Unitech COSPECT (University of Milan).