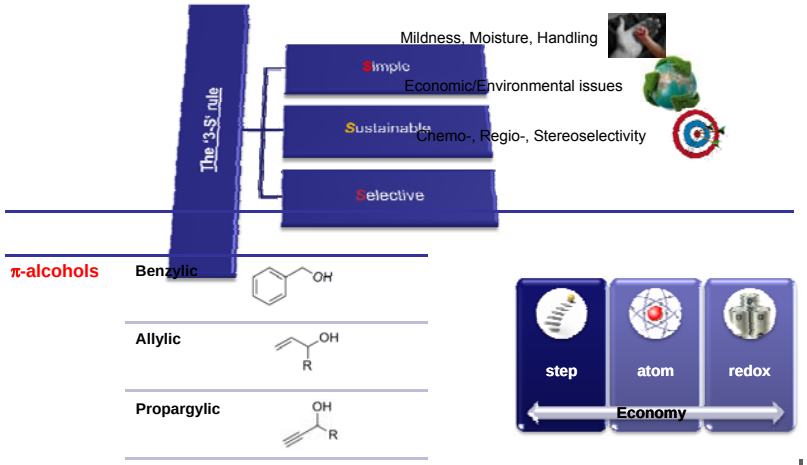
Marco Bandini
Dipartimento di Chimica "G. Ciamician"

Stereoselective gold-catalyzed manipulation of π-activated alcohols

IASOC- 2012

Organic synthesis today....



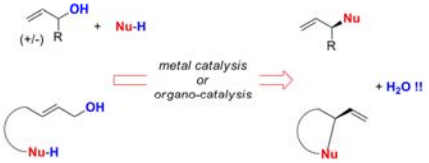
M. Rueping, et al. *Beilstein.J.Org.Chem.* **2010**, *6*, doi:10.3762/bjoc.6.6

π-Alcohols in Asymmetric Synthesis

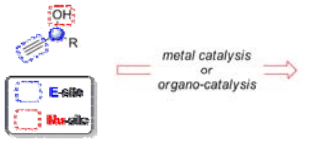
Allylic Alcohols

Nucleophilic allylic substitutions

S_N1-mechanism
η^3-intermediate (Tsuji-Trost)
M-η^2-activation



Propargylic Alcohols



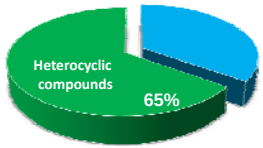
Propargylation
Allenylation
Cascade reaction

Recent reviews

- M.B., G. Cera, M. Chiarucci, *Synthesis*, **2012**, 504.
- A. Aponick, et. al. *Eur.J.Org.Chem.* **2011**, 6605.
- P.G. Cozzi, et al. *Eur.J.Org.Chem.* **2011**, 647.
- X.-L- Hou, et al. *Chem.Rev.* **2011**, *111*, 1914.
- M.B., M. Tragni, *OBC* **2009**, *7*, 1501.
- J. Muzart, *Eur.J.Org. Chem.* **2007**, 307.
- Y. Tamaru, Y. *Eur.J.Org.Chem.* **2005**, 2647

Rings and Hetero-rings in *Nature*

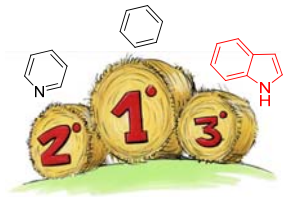
20.000.000 *Organic Compounds*



Bioactive molecules

96.7% (any rings)
65.2% (aliphatic rings)
75.6% (aromatic rings)

Abudance of aromatics in natural compounds



P. Ertl, *J.Med.Chem.* **2006**, *49*, 4568
M.B., A. Melloni, A. Umani-Ronchi, *ACIE* **2004**, *43*, 550

Indole in the AFCA realm

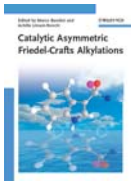
Indole (C3-position)
10^{13} times more nucleophilic than benzene

C3

Michael additions
Hydroarylations
Allylic alkylations
S_N2-type substitutions
Additions to carbonyls
Diels-Alder

Michael additions
Additions to carbonyls
Diels-Alder

C2



Wiley-VCH **2009**

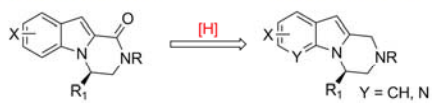
Catalytic enantioselective functionalization of the N(1)-atom:

unexplored
up to 2008 !!!

- **Chen** (Bayilis-Hillman, $DHQD)_2$-PHAL), ACIE **2009**
- **Hartwig** (Allylic alkylation, Ir) ACIE, **2009**
- **Enders** (Michael cascade, amino-catalysis) Synthesis, **2009**
- **Wang** (Michael cascade, amino-catalysis) ChemEurJ, **2010**
- **You** (Michael, BA catalysis; AAA, Ir-catalysis) ACIE, **2010, 2012**

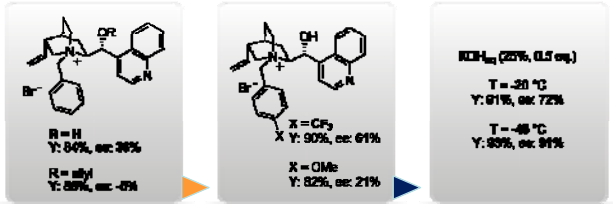
PTC-aza-Michael addition

Pyrazino-indolones → [H] → **Pyrazino-indoles**

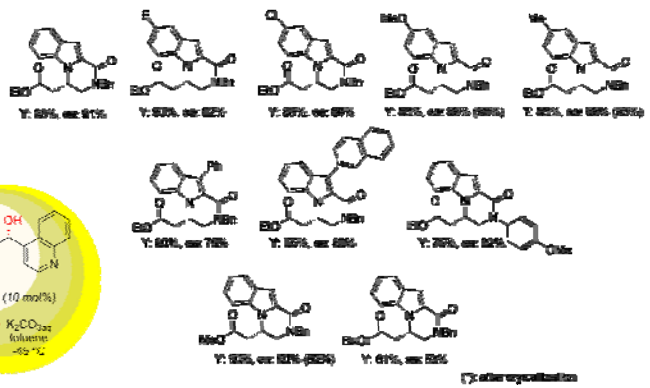


- antifungal
- noncompetitive antihistamine
- inhibition of serotonergic receptors
- antiobesity agents
- non insulin dependent diabetes

C-9 position | Benzyl group | T/base

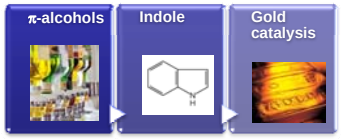


Scope of the reaction



Σ....ummary

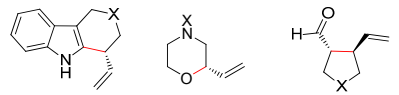
REACTIVITY-DRIVEN approach.....*indole platform*



- ***Chemical diversity***
- Target-oriented synthesis
- Methodology

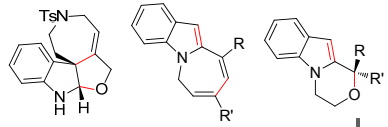
Allylic alcohols

- THCs, THBCs
- morpholines
- alkylation of aldehydes

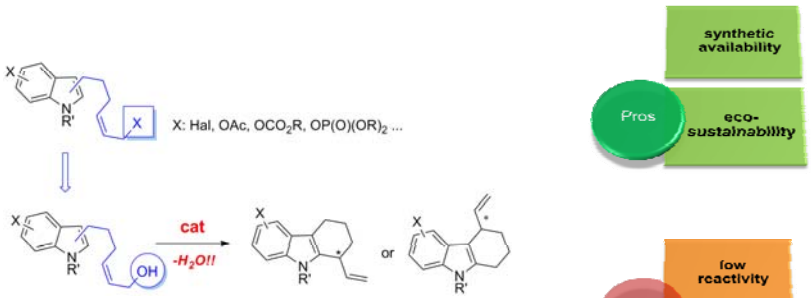


Propargylic alcohols

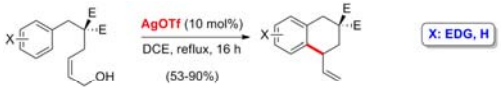
- Indolines
- Azepinoindoles
- Oxazinoindoles



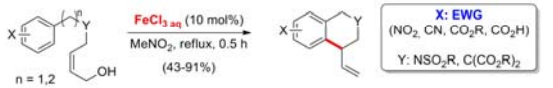
What about allylic alcohols?

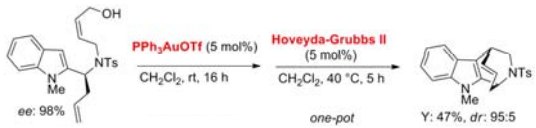


Preliminary studies with allylic alcohols

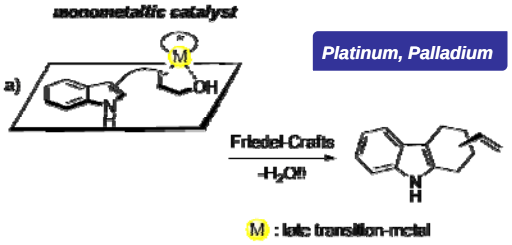


No moisture restrictions

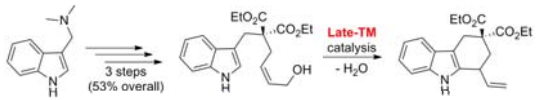




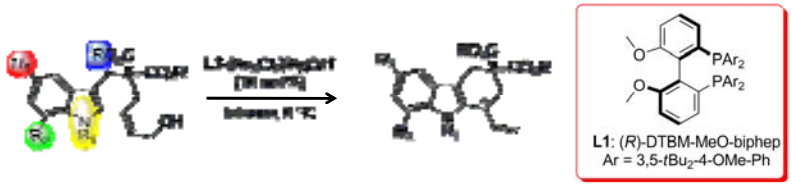
Enantioselective FC-type allylic alkylation with alcohols



Model reaction



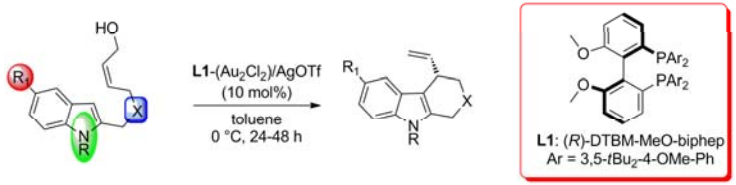
Synthesis of 1-vinyl-THCs



Entry	R/R1/R2/R3	Y (%)	Ee (%)
1	Et/H/H/Br	60	86
2	Et/H/H/Me	68	92
3	Et/H/H/OMe	61	96
4	Et/H/Me/H	91	83

Entry	R/R1/R2/R3	Y (%)	Ee (%)
5	Et/H/H/Cl	52	85
6	tBu/H/H/H	53	92
7	Et/H/H/OBn	78	82
8	Et/H/H/H	78	88

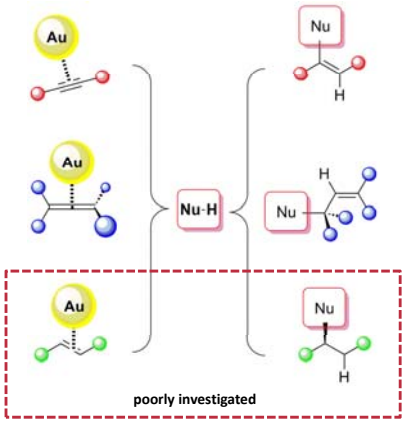
Synthesis of 4-vinyl-THCs and -THBCs



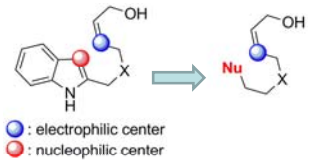
Entry	R/R$_1$/X	Y (%)	Ee (%)	Entry	R/R$_1$/X	Y (%)	Ee (%)
1	Me/H/C(CO$_2$Et)$_2$	79	86	6	Me/H/NTs	75	80
2	Me/H/C(CO$_2$tBu)$_2$	80	80	7	Me/Cl/NTs	93	79
3	Me/H/C(CO$_2$Me)$_2$	87	74	8	Me/Me/NTs	75	80
4	Me/OMe/C(CO$_2$Et)$_2$	55	83	9	Me/OMe	61	76
5	Me/Me/C(CO$_2$Et)$_2$	87	80	10	Allyl/H/NTs	72	78

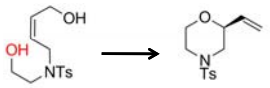
A. Eichholzer, M.B. *ACIE.* **2009**, *48*, 9533 (VIP article, Synfacts, **2010**, *3*, 313)
A. Romaniello, M.B. *J.Organomet.Chem.* **2011**, *696*, 338

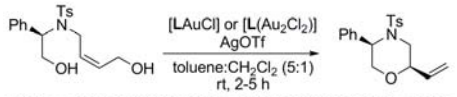
Electrophilic **Au(I)**-activation of alkenes: new opportunities in asymmetric catalysis



Intramolecular asymmetric allylic oxyalkylation





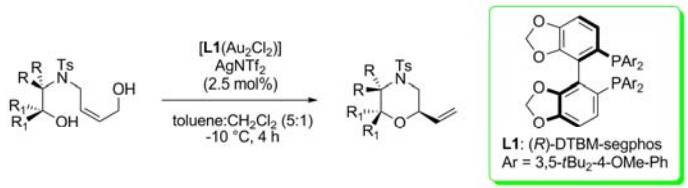


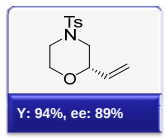
L1: PPh_3 L2: dppm L3: dppe L4: dppf

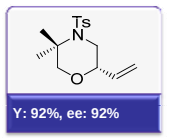
L	Cat (mol%)	Y (%)	dr
--	10	46	95:5
L1	10	95	83:17
L2	5	92	95:5
L3	5	89	95:5
L4	2.5	92	> 98:2
L4	0.8	70	98:2

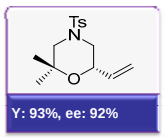
No moisture restrictions

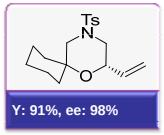
Enantioselective synthesis of vinyl-morpholines

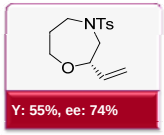


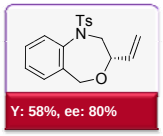






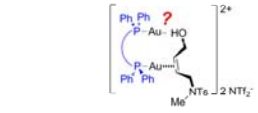






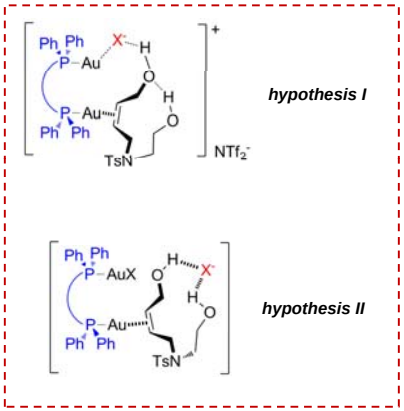
M. Tragni, *Chem.Eur.J.* **2010**, *16*, 14272.
(Synfacts, **2011**, *3*, 297).

Coordination mode insights

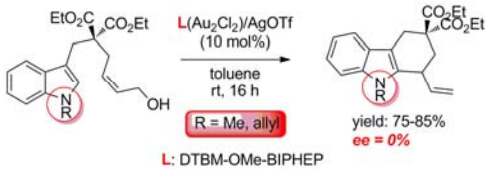


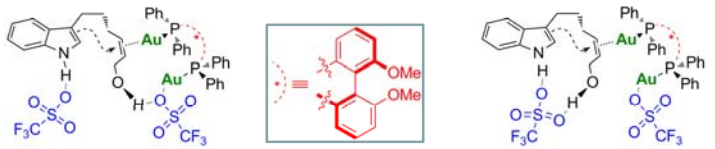
C=C configuration | H atom leaving OH | Au counterion

Key aspects



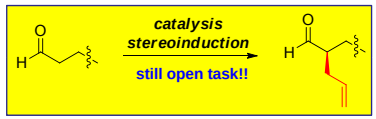
Coordination mode insights





G. Miscione, M.B. *submitted*

α-Allylic alkylation of aldehydes



Intramolecular approaches:

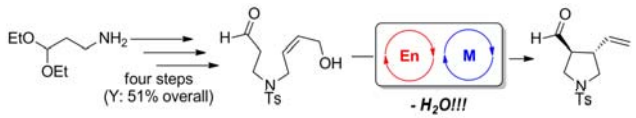
- MacMillan organocatalysis (sylanes-2011)
- Saicic Pd-catalysis (phosphates-2009)

Intermolecular approaches:

- List organo-metalcatalysis (amines-2007)
- Palomo organocatalysis (bromides-2011)

What about allylic alcohols ??

α-Allylic Alkylation of **Enolizable** Aldehydes with ***Primary*** Alcohols?

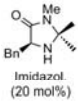


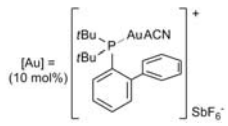
Org.Cat	M	Y (%)	Dr *(trans:cis)*	Ee (%)
Pyrrolidine (20%)	M (10%)	--		
Pyrrolidine	[Au]	75	11:1	--
Imidaz./$PhCO_2H$	[Au]	93	10:1	90

M: $In(OTf)_3$, $Bi(OTf)_3$, $Cu(OTf)_2$, $FeCl_3$, $Pd(PPh_3)_4$, $Zn(OTf)_2$, $biphepPt(OTf)_2$

reaction conditions: THF_{wet}, rt, 4 h

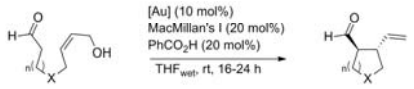
Organo-catalysis | Gold-catalysis





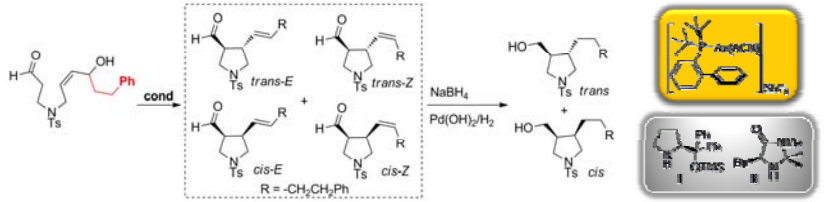
M. Chiarucci, M.B. *Chem.Sci.* **2012**, *3*, 2859-2863

Scope of the reaction



entry	X/n	Yield (%)	Dr *trans:cis*	Ee (%)
1	$C(CO_2Me)_2$/1	78	2.3:1	84 (84)
2	$C(CO_2tBu)_2$/1	90	2.6:1	91 (85)
3	$C(CO_2Bn)_2$/1	78	2.2:1	89 (88)
4	$C(CO_2Et)_2$/1	71	2.3:1	96 (85)
5	NSO_2Mes/1	53	5.1:1	94 (88)
6	NCO_2Me/1	53	9:1	98 (98)
7	NCbz/1	83	16:1	97 (85)
8	NTs/2	33	20:1	98 (-)

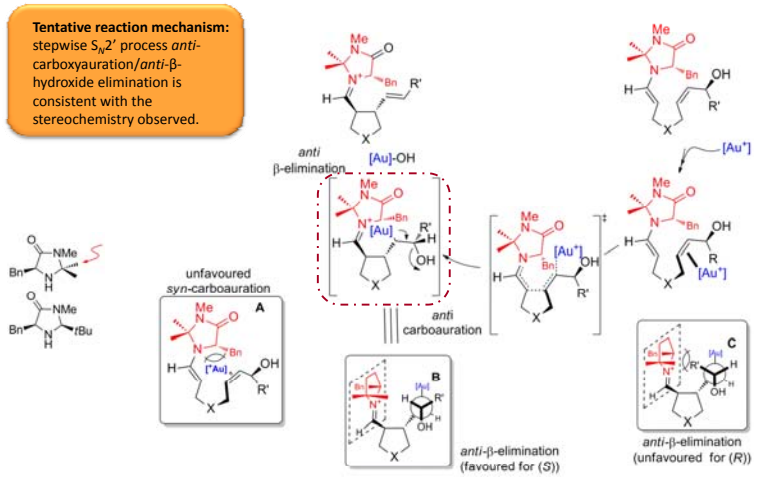
Secondary alcohols
Evidences for Kinetic Resolution



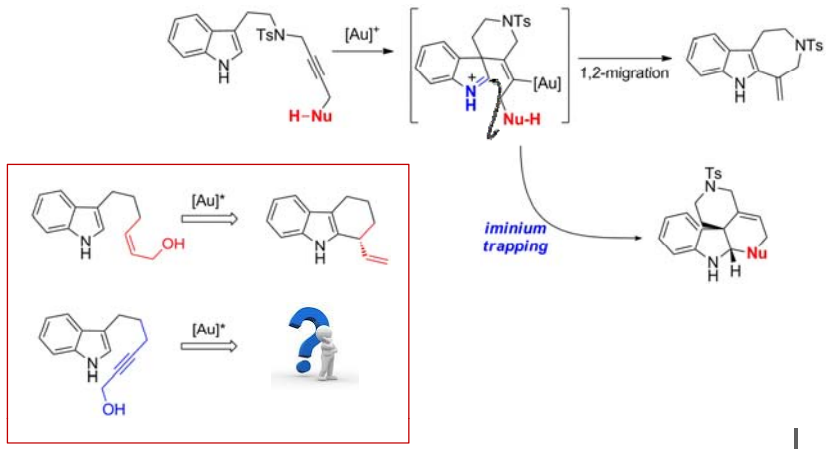
Run	Subst.	cat	Yield (%)	Dr *trans:cis*	*trans* (*E:Z*)	*cis* (*E:Z*)	Ee (%)
1	racemic	I	57	4.9:1	57:43	48:52	-30 (-31)
2	racemic	II	25	4:1	97:3	70:30	87 (82)
3	(*S*) [ee = 85%]	II	42	49:1	>99:1	75:25	98 (76)
4	(*R*) [ee = 84%]	II	traces	--	--	--	--

Reaction Machinery

Tentative reaction mechanism: stepwise S_N2' process *anti*-carboxyauration/*anti*-β-hydroxide elimination is consistent with the stereochemistry observed.

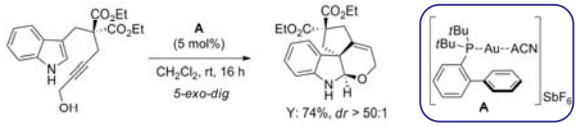


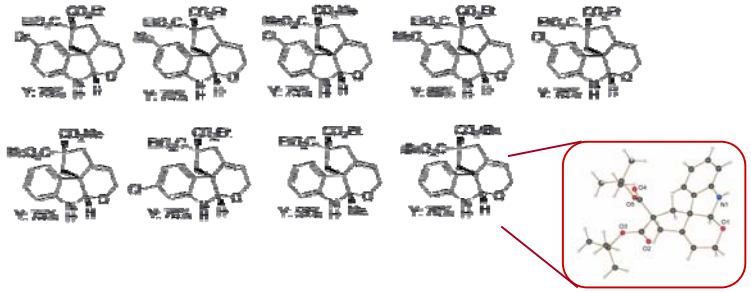
Gold Catalyzed Cascade Reactions: propargylic alcohols



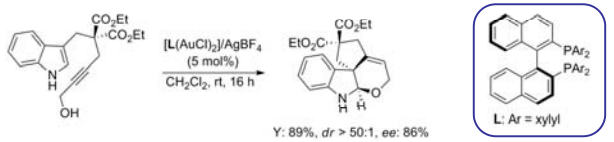
A. Echavarren, et al. *Chem.Eur.J.* **2007**, *13*, 1358
A. Echavarren, et al. *Tetrahedron* **2009**, *65*, 9015

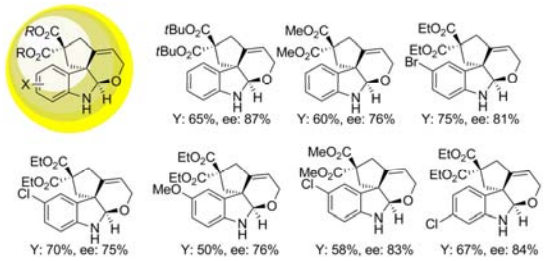
Gold-catalyzed synthesis of tetracyclic-fused indolines



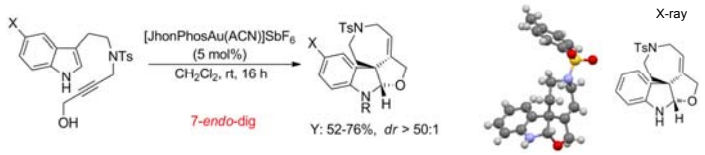


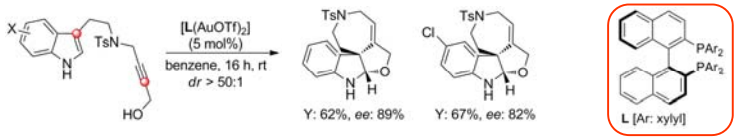
Enantioselective ***gold***-catalyzed cascade reactions



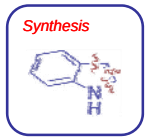


Enantioselective ***gold***-catalyzed cascade reactions: furo-indolines





One-pot *De novo* Synthesis and Functionalization of Indoles



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S.-L. You, *Chem.Soc.Rev.* **2009**, *38*, 2190
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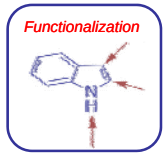
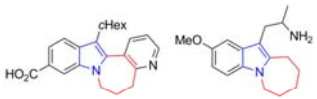
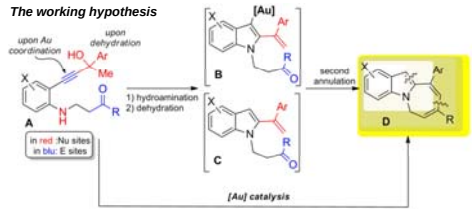
J. Barluenga, *Chem.Asian.J.* **2009**, *4*, 1036



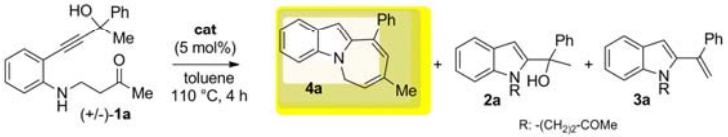
Azepino[1,2-a]indoles



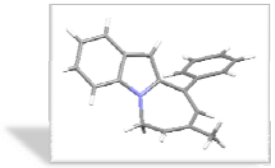
modulators for receptors of the CNS neurotransmitters



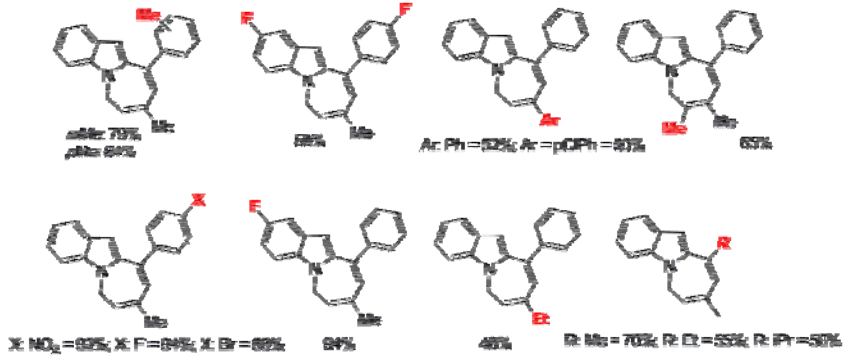
Optimization of the catalytic system



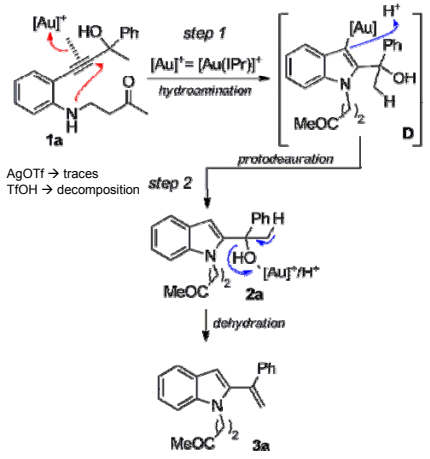
Entry	cat	Yield 2a (%)	Yield 3a (%)	Yield 4a (%)
1	$In(OTf)_3$	--	--	--
2	$FeCl_3$	--	--	--
3	AgOTf	--	--	--
4	TfOH	--	--	--
5	PPh_3AuNTf_2	64	36	--
6	$[(Ph_3Au)_3O]BF_4$	35	--	--
7	$XPhosAuNTf_2$	--	98	--
8	$JhonPhosAuSbF_6$	--	80	--
9	AuiPrCl/AgOTs		76	33
10	**AuiPrCl/AgOTf**	--	--	**96**

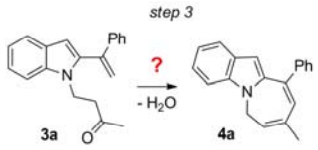


Scope of the reaction



The reaction machinery

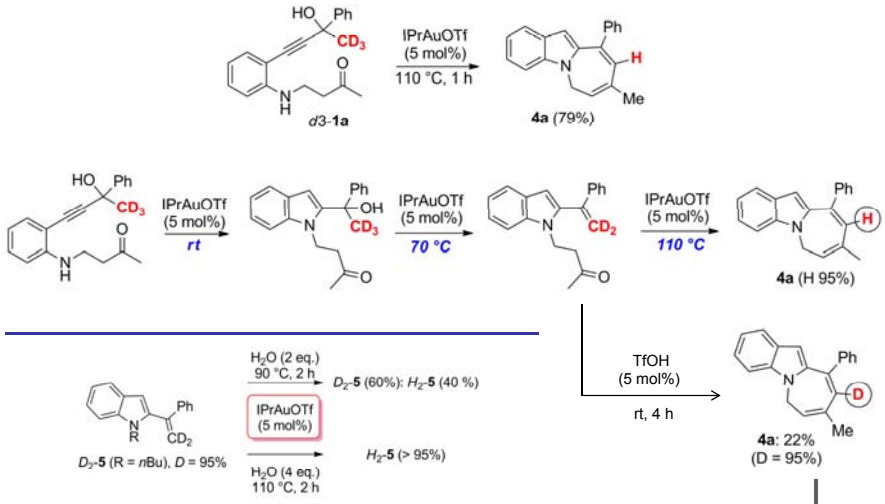




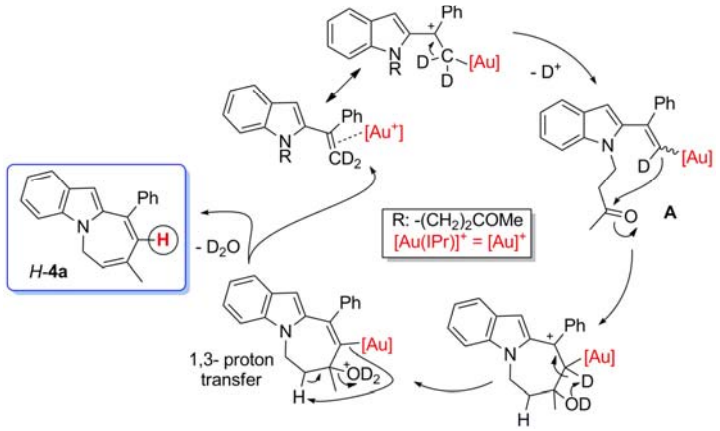
LA or BA-assisted
Prins-type cyclization?

[(PhO)$_3$PAuOTf] → traces
iPrAuOTf → 96% yield

The reaction machinery

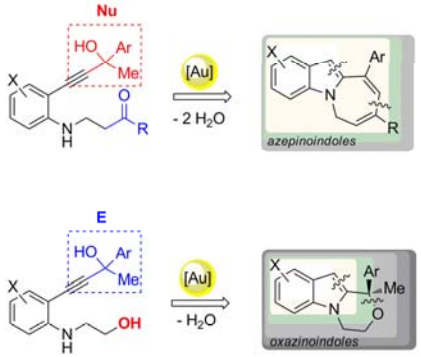


Tentative mechanistic rational



G. Cera, M.B. *Angew.Chem.Int,Ed,* in press selected as a 'Hot Paper'

Chemical flexibility of tertiary propargylic alcohols



i) Hydroamination *5-endo-dig*
ii) Alkoxyalkylation

M. Chiarucci, *unpublished*

Thanks to…

Present Members

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Elia Matteucci

Collaborations

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Prof. A. Bottoni
Prof. S.P. Nolan
Prof. G. Fabrizi

Consorzio CINMPIS