Asymmetric Catalysis

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Merging Synthesis and Enantioselective Functionalization of Indoles by a Gold-Catalyzed Asymmetric Cascade Reaction**

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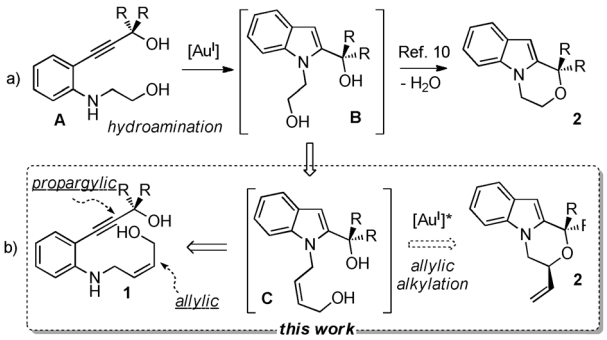
Indole chemistry continues to gain credit within organic synthesis owing to the ubiquitous presence of this heteroaromatic ring in pharmaceuticals, agrochemicals, and organic functional material science.[1] Over the past few years, metal and metal-free catalysis has played a major role in the area, contributing to the development of a number of sustainable procedures for both synthesis and asymmetric decoration of the indolyl core.[2–4]

Interestingly, up to now catalytic synthesis and enantioselective functionalization of the indole derivatives seemed to proceed on parallel routes,[5] and no examples of merging these reactivities, under the direction of a single chiral promoting agent, have been reported. Undoubtedly, providing reliable solutions to this still open issue will deeply impact crucial aspects of modern organic synthesis: step, redox, and atom economy in alkaloid chemistry.

In this direction, we recently reported the efficient combination of cationic gold catalysis[6] and π-activated alcohols[7–9] for the realization of chemical diversity/complexity in indole chemistry. In particular, by treating *ortho*-alkynylaniline diols **A** with achiral gold species, we accessed a library of oxazino-indoles **2** through the hydroamination/dehydrative alkoxylation synthetic sequence (Scheme 1 a).[10] The structure of the indolyl-diol intermediate **B**, in combination with the aptitude of chiral gold complexes in promoting stereoselective allylic alkoxylation reactions,[7f] inspired the possibility to synchronize synthesis and enantioselective decoration of indole derivatives by replacing the CH_2CH_2OH group of **A** with an allylic alcohol unit at the aniline nitrogen atom.[8c] This consideration prompted us to merge the chemistry of propargylic and allylic alcohols to access an important class of polycyclic indole compounds, such as the oxazino[4,3-*a*]indoles **2**, in a stereochemically defined manner.[11]



Scheme 1. Allylic and propargylic alcohols work synergically towards the one-pot gold-catalyzed synthesis of indolyl cores and subsequent enantioselective functionalization.

In particular, initial hydroamination of the triple bond would result into the formation of a benzylic alcohol intermediate **C** that could evolve into 1-vinyl-oxazino[4,3-*a*]indoles **2** by asymmetric nucleophilic allylic substitution (Scheme 1 b). Remarkably, this approach would lead to a new path towards the one-pot enantioselective synthesis of oxazino[4,3-*a*]indoles **2**, an important class of pharmacologically active alkaloid derivatives.[12]

It has to be emphasized that such a late-stage stereodifferentiating event in a gold-catalyzed asymmetric domino process is somehow unusual,[13] and the choice for a particularly robust and functional-group-tolerant catalytic system will be mandatory.[14]

During the optimization of the catalytic system, acyclic precursor **1a** was elected as the model substrate, and an extensive survey of reaction conditions was carried out (Table 1).[15]

A range of commercially available C2-symmetric chiral biphosphines (**L1**–**L9**) were tested (entries 1–9) in the presence of $AgNTf_2$ as the halide scavenger and toluene/CH_2Cl_2 (4:1) as the reaction media. Interestingly, the formation of the oxazino-indole **2a** was always preferred with respect to oxazocino[4,3-*a*]-indole derivative **2a′**, providing clear evidence of the preferred intramolecular allylic alkylation with respect to the dehydrative alkoxylation of the tertiary alcohol. Among them, promising results in terms of enantioselectivity and reaction rate were recorded with DTBM-segphos (**L9**) as the chiral ligand (5 mol%). In particular, after 4 h reaction time, **2a** was obtained in 64% yield, 95:5 **2a**/**2a′** ratio, and 72% *ee* (entry 9). Moreover, the impact of the counterion over the stereochemical profile of the process was investigated (entries 11–15). Bis(trifluoromethansulfonamide) emerged as the anion of election, while comparable results

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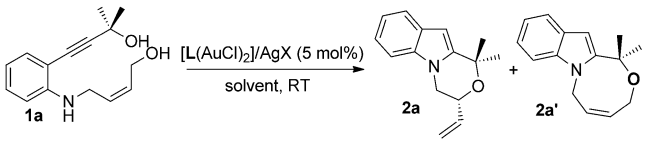
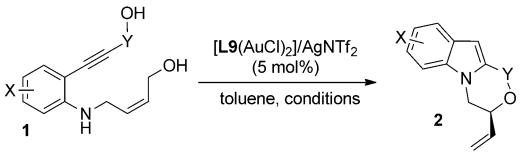
Table 1: Optimization of the catalytic system.[a]



Entry	L	X[b]	Solvent	2a/2a′[b]	Yield [%][c] 2a+2a′	ee [%][b] 2a
1	**L1**	NTf_2	Tol/CH_2Cl_2	–[d]	–	–
2	**L2**	NTf_2	Tol/CH_2Cl_2	95:5	46	4
3	**L3**	NTf_2	Tol/CH_2Cl_2	80:20	77	11 (–)
4	**L4**	NTf_2	Tol/CH_2Cl_2	>95:5	49	50
5	**L5**	NTf_2	Tol/CH_2Cl_2	>95:5	77[e]	54 (–)
6	**L6**	NTf_2	Tol/CH_2Cl_2	>95:5	60[f]	47 (–)
7	**L7**	NTf_2	Tol/CH_2Cl_2	>95:5	79[f]	48 (–)
8	**L8**	NTf_2	Tol/CH_2Cl_2	>95:5	77	58
9	**L9**	NTf_2	Tol/CH_2Cl_2	>95:5	64[f]	72
10	**L9**	NTf_2	Tol/CH_2Cl_2	80:20	47[g]	65
11	**L9**	ClO_4	Tol/CH_2Cl_2	20:80	58[f]	5
12	**L9**	OTs	Tol/CH_2Cl_2	60:40	72	11 (–)
13	**L9**	SbF_6	Tol/CH_2Cl_2	45:55	45[f]	63
14	**L9**	OTf	Tol/CH_2Cl_2	>95:5	70[f]	55
15	**L9**	NaBArF	Tol/CH_2Cl_2	85:15	83	9 (–)
16	**L9**	NTf_2	dioxane	>5:95	93	–
17	**L9**	NTf_2	toluene	>95:5	72[h]	85 (–)
18	**L9**	NTf_2	toluene	>95:5	72[i]	87 (–)

[a] All of the reactions were carried out under nitrogen for 24 h. Standard conditions require toluene/CH_2Cl_2 4:1 as the reaction media and room temperature. [b] Determined by chiral HPLC. [c] Yields of isolated product after flash chromatography. [d] No reaction. [e] Reaction time 2 h. [f] Reaction time 4 h. [g] With (*E*)-**1a**. [h] Reaction time 1 h, with (*R*)-**L9**. [i] Reaction time 16 h at 0°C, with (*R*)-**L9**. **L**: **L1** = (*R*)-binaphane; **L2** = (*R*)-diop, **L3** = (*R*)-Tol-binap, **L4** = (*S*)-3,5-xylyl-phanephos, **L5** = (*R*)-xylyl-SDP; **L6** = (*S*)-DTBM-MeO-biphep; **L7** = (*S*)-3,5-xylyl-MeO-biphep; **L8** = (*R*)-3,5-(*i*Pr)$_2$-4-NMe_2-MeObiphep; **L9** = (*S*)-DTBM-segphos.

Table 2: Scope of the reaction.[a]



Entry	Y	X[b]	Cond. [°C]/[h]	2	Yield [%][c]	ee [%][d]
1	*c*Hex	H	0/24	**2b**	72	84
2	*c*Hept	H	0/22	**2c**	94	78
3	$C(nC_4H_7)_2$	H	25/7	**2d**	72	84
4	CH_2	H	25/24	**2e**	88	85
5	$C(C_2H_5)_2$	H	25/4	**2f**	71	82
6	4-pyranyl	H	25/7	**2g**	74	86
7	4-(*N*Ts)piperidyl	H	25/4	**2h**	62	95
8	$C(Me)_2$	6-Cl	25/2	**2i**	61	82
9	$C(Me)_2$	5-CF_3	25/4	**2j**	84	86
10	$C(Me)_2$	5,7-$(Me)_2$	25/4	**2k**	93	90
11	4-(*N*Ts)piperidyl	6-Cl	25/24	**2l**	84	90
12	4-(*N*Ts)piperidyl	5-F	25/2	**2m**	78	96
13	4-(*N*Ts)piperidyl	5-CF_3	25/24	**2n**	62	95
14	4-(*N*Ts)piperidyl	5-Me	25/5	**2o**	82	94[e]
15	4-(*N*Ts)piperidyl	5,7-$(Me)_2$	25/24	**2p**	62	98
16	fluorenyl	H	25/92	**2q**	30	84

[a] All of the reactions were carried out under nitrogen with (*R*)-**L9**. [b] Position of the substituents is referred to the indole ring of **2**. [c] Yields of isolated product after flash chromatography. [d] Determined by chiral HPLC. [e] 4:1 toluene/CH_2Cl_2 was used as the reaction media.

in terms of stereodiscrimination were obtained also in the presence of SbF_6^- (63% *ee*, entry 13), accompanied by poor chemoselectivity (**2a**/**2a′** = 45:55). Finally, inversion of stereoinduction was recorded when OTs and BArF were employed (entries 12, 15).[16]

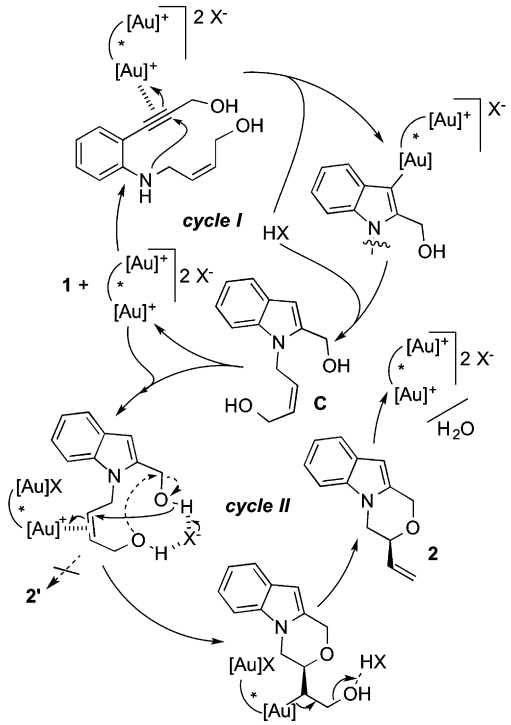
Then, a range of reaction media was assessed, indicating toluene as the solvent of choice. Delightfully, **2a** was obtained selectively (**2a**/**2a′** > 95:5) in 72% yield and with enantiomeric excess up to 87% at 0°C (entry 18). Notably, the importance of the C=C configuration over the whole reaction profile was finally investigated by subjecting (*E*)-**1a** to optimal reaction conditions ([DTBM-segphos$(AuNTf_2)_2$], toluene/CH_2Cl_2, RT). Interestingly, almost complete inversion of stereoinduction in the presence of the same enantiomer of the chiral ligand (−65% *ee*, entry 10) was recorded, providing a clear insight into the S_N2'-type mechanism of the final allylic alkylation ring closure.[7f,17] Last but not least, a range of acid–base additives and water scavengers were tested without any significant improvements in terms of both chemical as well as optical reaction outcome (see the Supporting Information for a complete list of results).

Then, with the optimal reaction conditions in hand, the scope of the procedure was evaluated by subjecting a range of diols (**1b**–**q**) to the [Au^I]-catalyzed cascade process (Table 2). Substituents were placed both on the alkynyl chain (Y) and in the aniline ring (X), providing a good level of functional-group tolerance. Generally, the presence of an alkyl group at the propargylic position increased the reaction rate in comparison to the unsubstitued propargylic derivative **1e** (entry 4). A classic Thorpe–Ingold effect[18] could be account to rationalize this behavior. Good to high enantiomeric excesses were routinely obtained with both cyclic as well as acyclic R-groups (78–90% *ee*). Interestingly, when *N*-tosyl pypirindone was chosen as the "tethering unit" X (**1h**, entry 7) the double ring-closing processes worked smoothly, providing **2h** in decent yield (62%) and excellent 95% *ee*. Then several anilines (**1i**–**p**) comprising substitutions at the benzenoid ring were explored. In all cases, the targeted oxazino-indoles were obtained in satisfactory yields (61–93%) and excellent stereocontrol (up to 98% *ee*).

Finally, the biaryl substituted fluorenyl diol **1q** was reacted under optimal reaction parameters. A prolonged reaction time (92 h) provided the corresponding polycyclic scaffold **2q** in modest yield (30%) but appreciable stereocontrol (entry 16).[19]

Absolute configuration of the final oxazino-indoles **2** was unambiguously determined to be *S*, by single-crystal X-ray analysis of compound **2h** (see the Supporting Information).[20]

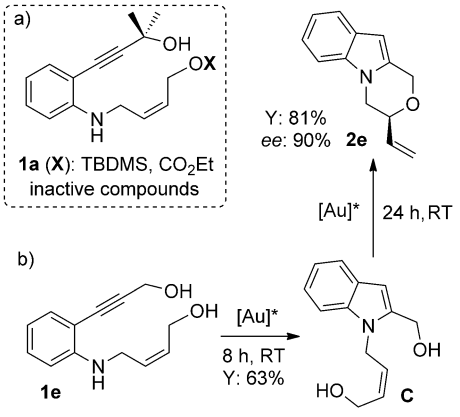
From a mechanistic point of view, the present [Au^I]-catalyzed cascade process can be rationalized as depicted in Scheme 2. In particular, the initial activation of the alkynyl unit by the chiral gold complex triggered the hydroaminative cycle followed by the protodeauration step (cycle I).[21] The resulting indolyl diol **C** can enter the stereoselective alkoxylation cycle (cycle II), which, based on recent mechanistic



Scheme 2. Mechanistic hypothesis for the gold-catalyzed synthesis of oxazino-indoles.

investigations on related transformations,[8d,e] is described as comprising a stepwise S_N2'-type process (that is, *anti*-alkoxyauration of the C=C, *anti*-elimination [Au]–OH sequence). Interestingly, reverse alkoxylation leading the tricyclic indole derivative **2′** became competitive or predominant to the allylating step only in highly coordinating solvents (such as dioxane).[19]

To shed some light on the proposed mechanism, the following experimental controls were carried out. First, the crucial role of the leaving hydroxy group on the overall process was ascertained by reacting under best conditions the corresponding *O*TBDMS and OCO_2Et derivatives of model substrate **1a** (Scheme 3a). Interestingly, in the case of the silyl



Scheme 3. Experimental controls. [Au]* = [(*R*)-DTBM-segphos-$(AuNTf_2)_2$] (5 mol%). DTBM = 3,5-di-*tert*-butyl-4-methoxy.

ether the complete consumption of the precursor led to a complex mixture of unknown compounds. On the contrary, ethylcarbonate underwent exclusively the initial C–N bond forming event (yield = 87%, RT, 16 h), demonstrating the complementarity of the gold-catalyzed allylic alkylations with respect to Pd-catalyzed Tsuji–Trost-like processes.[22,23] Finally, we unambiguously confirmed the role of diol **C** as the molecular conjunction of the two catalytic cycles by stopping the cascade reaction of **1e** after 8 h (**C** was isolated in 63% yield). Then, indolyl diol **C** was reacted in the presence of DTBM-segphos$(AuNTf_2)_2$ (5 mol%), leading to **2e** with stereoinduction (yield = 81%, 90% *ee*), which is comparable to the one-pot procedure (Table 2, entry 4, 85% *ee*; Scheme 3b).

In conclusion, we have documented an unprecedented stereoselective gold-catalyzed cascade sequence to access substituted oxazino-indoles in high enantiomeric excess, exploiting simultaneously the synthetic flexibility of allylic and propargylic alcohols. Interestingly, the use of a single chiral gold complex assisted both synthesis of the pyrrolyl core and the subsequent enantioselective allylic alkoxylation, delivering water as the only by-product.

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