Enantioselective gold catalyzed dearomative [2+2]-cycloaddition between indoles and allenamides

Enantioselective Gold Catalyzed Dearomative [2+2]-Cycloaddition between Indoles and Allenamides

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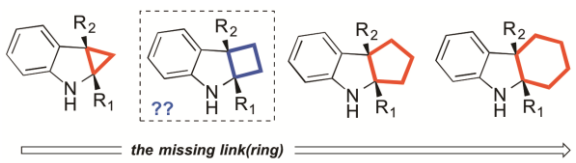
The highly enantioselective synthesis of densely functionalized 2,3-indoline-cyclobutanes by means of chiral gold catalysis is presented. Intermolecular formal [2+2]-cycloaddition reactions between substituted indoles and allenamides enabled direct access to methylenecyclobutane-fused indolines, featuring two consecutive quaternary stereogenic centers with excellent stereochemical control (dr > 20:1, ee up to 99%).

Functionalized polycyclic fused indoline scaffolds are central molecular architectures in biologically active heterocyclic compounds and organic electronics.[1] In this context, the stereoselective dearomatization reaction of indoles represents a modern and powerful tool to access polycyclic C2,C3-fused indoline motifs starting from readily accessible precursors.[2] Among the numerous catalytic methodologies recently developed,[3] the enantioselective C2,C3-annulation of indoles via cycloaddition reactions[4] is gaining growing credit in terms of chemical efficiency. Based on these methodologies, densely functionalized C2,C3-fused cyclopropa-([2+1]), cyclopenta-([3+2]) and cyclohexa-indoline cores ([3+3]) have been prepared in stereochemically defined manners (Figure 1).

However, despite great efforts in this field, direct catalytic enantioselective protocols to address cyclobuta-fused indoline skeletons[5] are still absent in the literature, and even the racemic [2+2]-dearomatization of indoles has been rarely studied.[6] Furthermore, [Au(I)]-mediated catalysis[7] was proved to be a powerful tool in the synthesis of cyclic compounds,[8] in which formal [2+2] cycloaddition reaction efficiently provided the valuable cyclobutane derivatives.[9] To be mentioned that the first example of intermolecular [Au(I)]-assisted asymmetric [2+2] cycloaddition between allenamides and alkenes was recently reported by Gonzáles and coworkers.[9f]

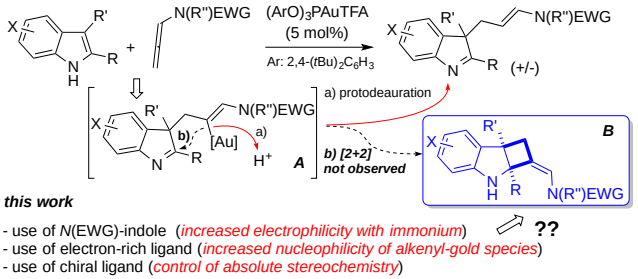
Figure 1. State of the art in the 2,3-fused indolenyl scaffolds – the missing link



In accordance with our scientific program focusing on the [Au(I)]-mediated functionalization of indoles,[10] we recently documented the [phosphite-Au(I)TFA] promoted site-selective C-3 functionalization of 2,3-disubstituted indoles with allenamides.[10k,11]

In this process, the final proto-demetalation quenched the alkenyl-gold intermediate ***A*** and restored the gold catalyst (path a). Based on that, we envisioned the possibility to prevent the protodeauration by a careful adjustment of both structure of the reaction partners and electronic properties of the gold-catalysts. In particular, the combined use of i) indoles carrying EWG at the *N*(1)-position (enhanced electrophilicity of the dearomatized indolenine intermediate) and, ii) electron-rich phosphines (increased nucleophilicity of alkenyl-gold species) could favor a second ring-closing event (path b), delivering the formal [2+2]-adduct ***B*** (Scheme 1).

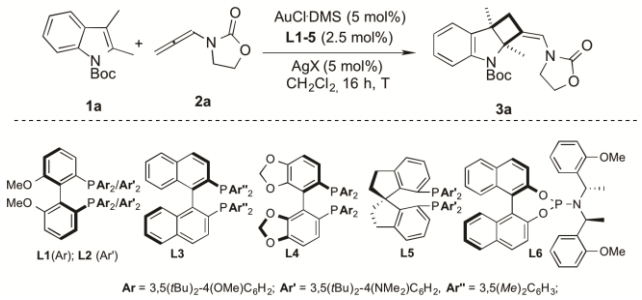
Scheme 1. Reaction design.



At the outset, *N*(Boc)-2,3-(Me)$_2$-indole **1a** and allenamide **2a** were elected as model substrates and subjected to a survey of reaction conditions (Table 1). Several mono- and bidentate chiral ligands **L1-L6**[7] were investigated initially (entries 1-6). Delightly, commercially available (*R*)-DTBM-segphos (**L4**, 2.5 mol%) furnished the desired diastereomerically pure [2+2]-cycloadduct **3a** in moderate yield (46%) and promising enantiomeric excess (76%, entry 4).

The effect of the counterion was then analyzed (entries 7-10, Table 1) electing OTf$^-$ as the best anion. In particular, although comparable results were achieved with AgNTf$_2$ as a halide scavenger, significantly lower conversions in **3a** were recorded with AgSbF$_6$, AgTFA and NaBArF. Finally, both chemo- and stereocontrol were dramatically improved by lowering the reaction temperature to -60 °C. Under these conditions, compound **3a** was obtained in quantitative yield (95%) as a single diastereoisomer[12] and synthetically acceptable ee (93%, entry 12).[13] Furthermore, increasing the catalyst loading to 5 mol% did not significantly modify the reaction outcome (entry 13).

Table 1. Optimization of the catalytic system.[a,b]



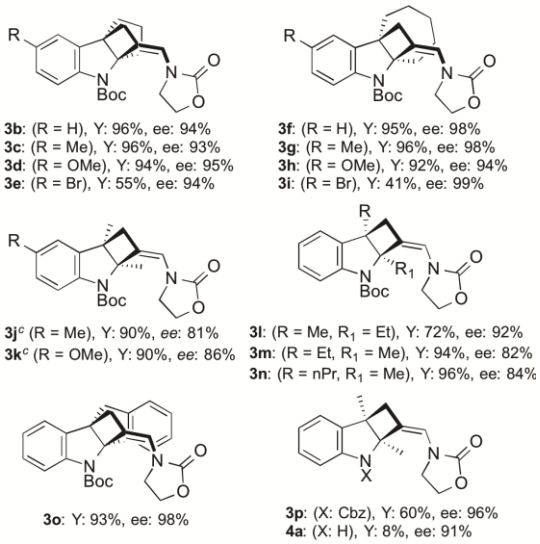
Run	L	AgX	T (°C)	Yield (%)[c]	Ee (%)[d]
1	(*S*)-**L1**	AgOTf	25	20	-17
2	(*S*)-**L2**	AgOTf	25	18	-2
3	(*R*)-**L3**	AgOTf	25	15	13
4	(*R*)-**L4**	AgOTf	25	41	76
5	(*R*)-**L5**	AgOTf	25	57	-27
6	(*R*,*S*,*S*)-**L6**	AgOTf	25	20	2
7	(*R*)-**L4**	$AgNTf_2$	25	30	76
8	(*R*)-**L4**	$AgSbF_6$	25	<5	74
9	(*R*)-**L4**	AgTFA	25	<5	--
10	(*R*)-**L4**	NaBArF	25	5	78
11	(*R*)-**L4**	AgOTf	-20	60	85
12	(*R*)-**L4**	AgOTf	-60	95	93
13[e]	(*R*)-**L4**	AgOTf	-60	95	92

[a] Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), in a CH_2Cl_2 solution (1.0 mL) of *in situ* formed **L**$(AuCl)_2$ complex (2.5 mol%). [b] Only one diastereomer was observed by NMR (dr > 20:1). [c] Determined after flash chromatography. [d] Determined by HPLC. [e] Catalyst loading of *in situ* formed (*R*)-**L4**$(AuCl)_2$ (5 mol%).

Having established the optimal catalytic system, the scope of the methodology was ascertained by subjecting a range of diversely substituted indoles (**1b-p**) to the best reaction parameters.[14] A collection of results is depicted in Table 2.

Remarkably, 2,3-annulated indoles featuring C5 and C7-membered rings (**1b-e,o** and **1f-i**, respectively) proved competent in the present protocol providing the corresponding methylenecyclobuta-indoline derivatives **3b-i,o** in excellent enantiomeric excess (93-99%) and synthetically acceptable yields (41-96%). In these cases, erosion in the chemical yields was recorded in the presence of 5-Br indoles **1e,i**. Substituents comprising linear alkyl chains of different lengths were also placed at the C(2) and C(3)-position of the indolyl core (**1l-1n**), obtaining satisfactory results in terms of optical outcome (ee: 82-92%). Finally, the pivotal role played by the electron-withdrawing group (*i.e.* Boc) over the reaction course was highlighted, by reacting the *N*-free-2,3-dimethylindole under optimal reaction parameters. Here, despite unaltered stereochemical profile was detected (ee = 91%), the final indoline **4a** was isolated only in 8% yield, which highlighted the importance of introducing a *N*-EWG group.[15] Accordingly, the Boc-activating group was also efficiently replaced by Cbz-(carboxybenzyl), delivering the corresponding tricyclic compound **3p** in satisfactory yield (60%) and excellent enantiomeric excess (96%). Unsubstituted or partially substituted *N*Boc-indoles were also examined with preference in delivering the C(2) or C(3)-Friedel-Crafts products in low conversion (see SI).

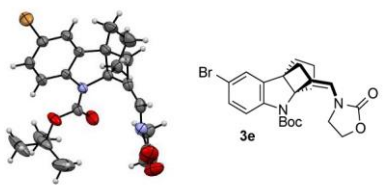
Table 2. Scope of the reaction.[a,b]



[a] Reaction conditions: **1**/**2a**/**L4**/AuCl-DMS/AgOTf: 1.2/1/0.05/0.1/0.1 in CH_2Cl_2 (1.0 mL) at -60 °C for 16 h. [b] In all cases, only one diastereomer was observed by NMR (dr > 20:1). [c] **1**/**2a**/**L4**/AuCl-DMS/AgOTf: 1.2/1/0.025/0.05/0.05.

The absolute configuration of the cycloaddition products was determined to be (*2aS,7bR,Z*) by means of single crystal diffraction study of enantiopure **3e** (Figure 2).[16]

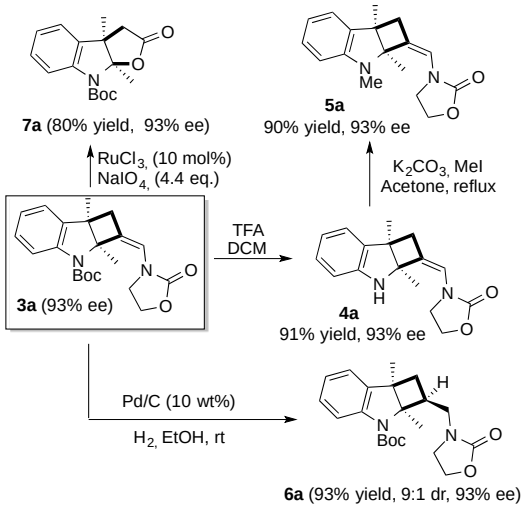
Figure 2. Determination of the absolute configuration of **3e** via X-ray crystallography



Finally, the synthetic flexibility of the [2+2]-cycloadducts **3** was investigated by subjecting enantiomerically enriched **3a** (*ee* = 93%) to a series of chemical manipulations (Scheme 2).

In particular, the selective removal of the *N*-Boc protecting group was efficiently achieved by treating **3a** with TFAH (TFAH: trifluoroacetic acid) in DCM. The corresponding *N*-free indoline **4a** was obtained with unaltered enantiomeric excess in good yield (91%). The chemical stability of indoline **4a** was verified by the treatment with K_2CO_3/MeI in refluxing acetone. The desired product *N*-methyl derivative **5a** was obtained in 90% yield and 93% *ee*.

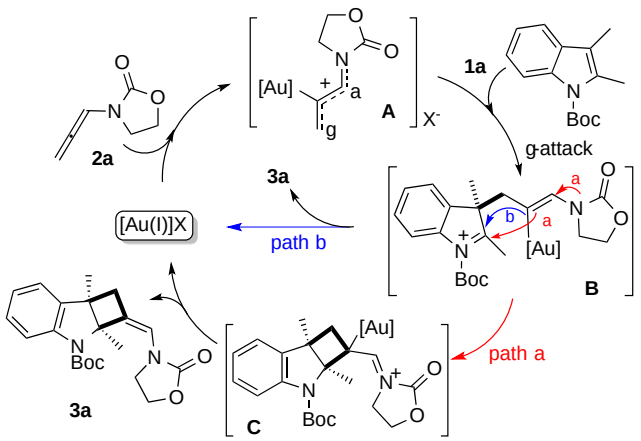
Scheme 2. Synthetic manipulations of **3a**



A new stereogenic center was also realized by means of diastereoselective hydrogenation of the enamidic C=C bond with Pd/C (10 wt%, H_2 1 atm). **6a** was isolated in yield = 93%, dr = 9:1 and ee = 93%. Finally, the enamide moiety was also demonstrated to be a valuable precursor of cyclic esters via site-selective oxidative cleavage of the C=C double bond by means of $RuCl_3/NaIO_4$ (CCl_4/H_2O). The resulting lactone **7a** was isolated in 80% yield and without any loss in enantiopurity (*ee* = 93%).

Focusing on the reaction mechanism, the catalytic cycle depicted in Scheme 3 is proposed. In particular, the initial coordination of the allenamide **2a** by the chiral cationic gold complex would lead to the electrophilic intermediate **A**. Then *N*(Boc)-2,3-$(Me)_2$-indole **1a** could attack regioselectively at the γ-position of **A** providing the gold-alkenyl intermediate **B**. At this stage, two different reaction channels can be envisaged. Pathway a) involves a second ring-closing event based on the nucleophilicity of the enamine moiety, and resulting in the alkyl-gold intermediate **C**.

Scheme 3. Proposed catalytic cycle.



The final rearrangement will then restore the catalytic species, providing the final compound **3a**. Alternatively (path b), the final cyclobutane **3a** could be directly obtained by **B** in a concerted like pathway. Here, the high stereoselectivity observed in the second ring-closing event (*i.e.* formation of the *exo*-C=C double bond with configuration *Z*) led to propose the concerted-like reaction channel b as the most likely way.

Conclusions

In summary, the first enantioselective gold catalyzed dearomative [2+2]-cycloaddition between indoles and allenamide **2a** is reported with high yield and excellent stereochemical control. The resulting chiral methylenecyclobutanes demonstrated competent building blocks in organic synthesis with several effective transformations. The mild reaction conditions, readily accessible starting materials, commercially available ligand and excellent stereocontrol make the current methodology particularly attractive in future synthesis of polycyclic indole based alkaloids.

Notes and references

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