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Convenient synthesis of polycyclic N(1)-C(2)-fused oxazino-indolones via [Au(I)] catalyzed hydrocarboxylation of allenes

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A new [Au(I)] catalyzed intramolecular hydrocarboxylation of allenes is presented as a valuable synthetic route to oxazino-indolones. The employment of 3,5-$(CF_3)_2$-C_6H_3-ImPyAuSbF$_6$ as the optimal catalyst (5 mol%) was necessary to guarantee i) wide tolerance of functional groups, ii) mild reactions conditions (rt, 16 h), and iii) high yields (up to 90%). Preliminary attempts towards an enantioselective version (80:20 *er*) were also documented by means of a new family of chiral C_1-symmetric ImPyAuCl complexes.

The development of sustainable synthetic methodologies for the realization of N(1)-C(2)-polycyclic fused indolyl scaffold is currently receiving growing credit in the chemical community.[1] In particular, 3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indol-1-ones (*i.e.,* oxazino-indol-1-one scaffold, **A**) keep stimulating progresses in organic synthesis due to their wide presence in bioactive compounds, naturally occurring species and as precursors of pharmacologically active ingredients (Figure 1a).[2] Nowadays, the available synthetic routes to the titled scaffold commonly require harsh reaction conditions (*i.e.,* high temperatures)[3] and/or stoichiometric additives (*i.e., halogens, $AgNO_3$*)[2e,4] and led to moderately functionalizable polycyclic-fused indolyl scaffolds (Figure 1b). On the contrary, the use of a catalytic approach has never been adopted for building up oxazino-indolone cores, to date.[5] Additionally, catalytic asymmetric variants are unprecedented so far.

Aiming at addressing the afore-described gap in the literature, we envisioned the development of an intramolecular condensation of readily available indole-2-carboxylic acids featuring *N*-tethered allenyl units **1**. (Figure 1c).[6] This approach would lead to a direct access of 3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indol-1-ones **2** possessing a tertiary stereogenic center and carrying a synthetically versatile vinyl unit.

Certainly, the direct use of unprotected carboxylic acids as nucleophilic partners could introduce some constrains in terms of metal catalyst design, therefore, our attention moved to the use of poorly oxophilic but π-acidic metal species. In line with our research results on the development of "on-demand" Au(I) catalysts, some of us have recently documented on the high performance of the CF_3-aryl-ImPy-based gold complex **Cat1** in the electrophilic manipulation of several π-systems (Figure 1d).[7] This peculiar catalytic activity was rationalized based on secondary interactions regarding the cationic alkenyl-[Au(I)]-type intermediates similar to **B**.

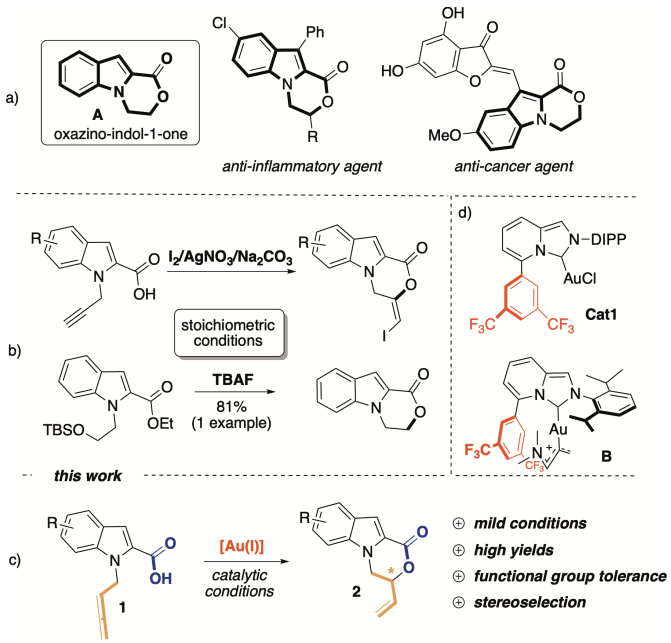

Figure 1. a) Examples of bioactive compounds based on the targeted oxazino-indole-1-one core **A**. b) Stoichiometric synthetic routes towards oxazino-indol-1-ones – State of the art. c) Au(I)-catalyzed hydrocarboxylation of allenes.

These findings, combined with our recent interest towards [Au(I)]-assisted synthesis of polycyclic fused indolyl cores,[8] prompted us to verify the efficiency of **Cat1** in the model hydrocarboxylation reaction of **1a** (Figure 1c, R = H). Interestingly, although gold catalyzed reactions of unactivated allenes, via C–C, C–N and C–O (mainly alcohols) bond forming protocols, have been extensively explored,[9] Au(I) catalyzed hydrocarboxylations of cumulenes have faced far less success in the literature with applications merely related to the preparation of γ-butyrolactones.[10]

At the outset of the investigation, an extensive survey of reaction parameters was underpinned to determine the optimal conditions (see ESI for details). Among the tested ligands, a family of ImPy[11] nitrogen heterocyclic carbenes (NHCs),[12] comprising diverse substitutions at the C(5)-position was considered (Figure 2a). In this context, besides the already documented gold complexes **Cat1,5,6**, three new dimethyl amino-based ImPy scaffolds were targeted (**Cat2–4**) in order to assess potentially key hydrogen bond interactions during the ring-closure. Here, complexes **Cat2,4,6** were accessible in high yields (96–99%) via direct condensation of the imidazopyridium salt precursors (**ImPy2–4**) with [AuCl·DMS] in acetone and K_2CO_3 in acetone.[13] Furthermore, the new complexes **Cat2–4** were fully characterized also via X-ray diffraction and the

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resulting molecular structures are reported in the Figure 2b. The arene···Au distance, that has been already proved to qualitatively predict the catalytic activity of the Au complexes in electrophilic activation of π-systems, was investigated for **Cat2** and **Cat3**.[7] These two pre-catalysts with electron-rich functionalization displayed higher arene···Au *vs* **Cat6** (3.352 Å) and a shortening of distance was noted for *meta*-substituted arenes *vs para*-ones (3.623 Å *vs* 3.566 Å). Furthermore, both –NMe_2 group have a high degree of planarity, due to the conjugation with the phenyl ring (see SI). On the contrary, complex **Cat4** showed a marked pyramidalization of the nitrogen atom of the –NMe_2 group, revealing a tight interaction with the metal centre (N(3)-Au 3.112 Å).

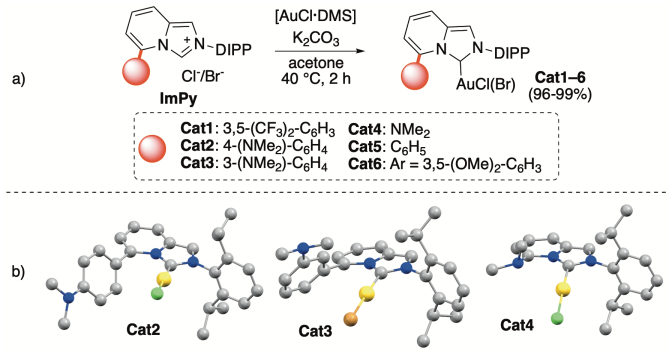
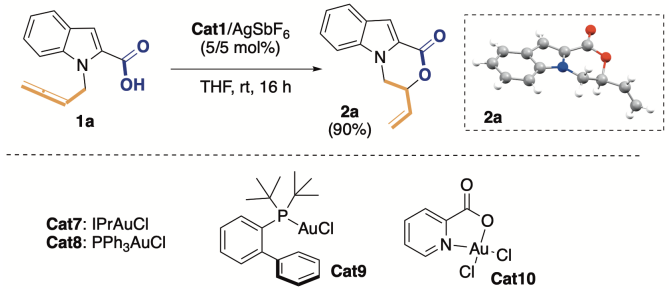


Figure 2. a) Collection of C(5)-functionalized ImPyAuCl/Br complexes used in this study. b) Single X-Ray structures of complexes **Cat2–4.**

Delightly, **Cat1** (5 mol%) proved high efficiency in the methodology by performing the chemo- and regioselective ring-closure of **1a** leading exclusively to the six-membered product **2a** in 90% isolated yield (5 mol% $AgSbF_6$, [**1a**] = 0.1 M in THF, rt). Variations on the electronic properties of the C(5)-aryl-pendants did not impact on the chemical outcome dramatically (82–90%, entries 1–5), with the only exception of 3,5-$(MeO)_2$-C_6H_3-PyIm(Au)Cl complex **Cat6** that produced **2a** in a lower extent (72% yield, entry 6).

Table 1. Optimization of the reaction conditions



Entry[a]	Deviation from optimal	Yield **2a** (%)[b]
1	–	90
2	**Cat2**	87
3	**Cat3**	83
4	**Cat4**	82
5	**Cat5**	83
6	**Cat6**	72
7	**Cat7**	69
8	**Cat8**	42
9	**Cat9**	< 5
10[c]	**Cat10**	< 5
11	**Cat1**/AgTFA	traces
12	**Cat1**/NaBArF	traces
13	**Cat2**/AgOTs	27
14	No $AgSbF_6$	NR
15	$AgSbF_6$ without **Cat1**	NR
16	Toluene	36
17	CH_3CN	NR
18	CH_2Cl_2	63

[a] Reaction conditions: **1a** (0.1 mmol, 0.1 M), under nitrogen atmosphere at rt. [b] Determined after flash chromatography as an average of two runs. [c] Using 10 mol% of $AgSbF_6$. NR: no reaction.

Interestingly, the family of ImPyAuCl catalysts proved remarkably superior with respect to IPrAuCl/$AgSbF_6$ (entry 7), and **2a** was obtained in 69% yield in 16 h. Additionally, the catalytic performance of the present ImPyAuCl complexes were also compared to benchmark *P*-based gold(I) catalysts, such as PPh_3AuCl (**Cat8**) and JohnPhosAuCl (**Cat9**).
Overall, phosphine-based ligands proved inefficient in the model reaction, providing **2a** in 42% yield and traces, respectively (entries 8 and 9). Similarly, a disappointing outcome was recorded using $picAuCl_2$ (**Cat10**, entry 10).

The genuine cationic gold catalysis was demonstrated by running the model protocol in absence of an Ag salt (entry 14) and a Au(I) complex (entry 15), resulting to no conversion in both cases. Finally, other parameters, such as gold counterion and reaction media, were investigated but no improvements with respect to the optimal conditions were recorded (entries 11–18).

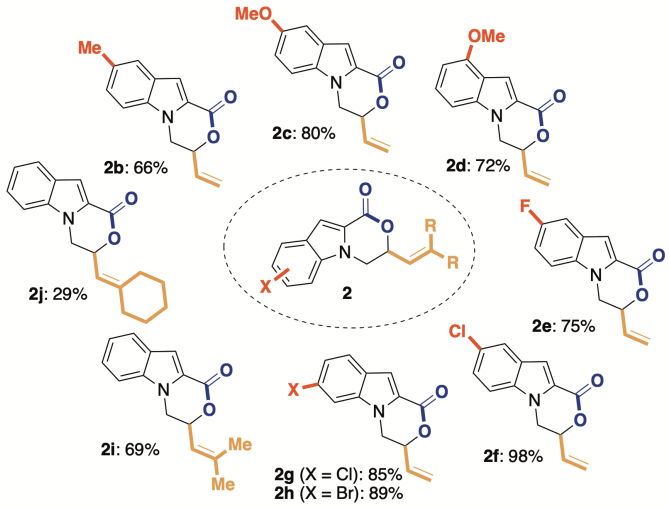
The catalytic performance of the C(5)-aryl-containing complexes **Cat1–3** and **Cat6** was analysed in comparison to the relative Ar…Au distances recorded at the solid state (Figure 3)
Interestingly, in the short series of electron-rich arene containing species (*i.e.*, **Cat 2,3** and **Cat6**) the arene/metal contact resulted as shorten as higher the strength of EDGs, with the *meta* substitution predominating over the *para*-ones (see **Cat2** *vs* **Cat3**). In particular, strongest interactions resulted in a lower catalytic performance (from 87% to 72%) and this output is ascribable to the stabilization effect of the EDG units on cationic organometallic intermediates formed upon Au-activation of the cumulene group of **1**. On the contrary, the destabilizing role played by the *meta*-substituted ring (3,5-$(CF_3)_2$-C_6H_3) on cationic organogold intermediates speeded-up the ring-closing event resulting in 90% isolated yield of **2a**.

Cat	Cat1 3,5-$(CF_3)_2$	Cat2 4-NMe_2	Cat3 3-NMe_2	Cat6 3,5-$(OMe)_2$
Ar.....Au (Å)	3.352	3.623	3.566	3.353
Yield **2a** (%)	90	87	83	72

EDG strenght

Figure 3. Ar...Au distance/catalytic performance correlation for C(5)-aryl substituted ImPy–Au complexes.

Therefore, the generality of the protocol was verified by subjecting a range of readily accessible and diversely substituted *N*-allenyl-indole-2-carboxylic acids **1b–j** to optimal C–O ring-closure conditions (Scheme 1, see SI for synthetic details) to the optimal conditions. Remarkably, electron-donating groups (Me, OMe) could be conveniently accommodated both at C(4) and C(5) positions of the benzenoid ring by providing the desired compounds **2b–d** in good to excellent yields (66–80%). Analogously, electron-withdrawing substituents at the indole core (*i.e.*, F, Cl and Br) were adequately tolerated (*i.e.*, C(5) and C(6) positions) providing the corresponding oxazino-indolones **2e**–**h** in very high yields (75–98%). Finally, the use of trisubstituted allenyl units as starting materials **1i,j** was assessed. Here, although the sterically congested *c*Hex-substituted allenyl framework (**1j**) caused a significant drop in conversion (**2j,** 29% yield), the use of *gem*-Me_2-substituted precursor **1i** yielded the desired tricyclic scaffold **2i** in synthetically useful 69% yield.



Scheme 1. Scope of the [Au(I)] catalyzed ring-closing reaction.

On the other hand, the procedure faced also some limitations in substrate scope. As a matter of fact, attempts to extend the process to differently structured seven-membered rings (**2m,n**) or pyrrolyl-2-carboxylic acid **1o** resulted in modest conversions (ca. 12–18% yield).[14]

Based on these promising results, we then turned out attention towards the development of an unprecedent catalytic enantioselective variant of the synthesis of 3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indol-1-ones. In this direction, we decided to preserve the ImPy ligand core in order to guarantee synthetically useful catalytic turnovers and we accommodated stereochemical information at the C(5)-position, that is known to be in close proximity with the reaction centre.

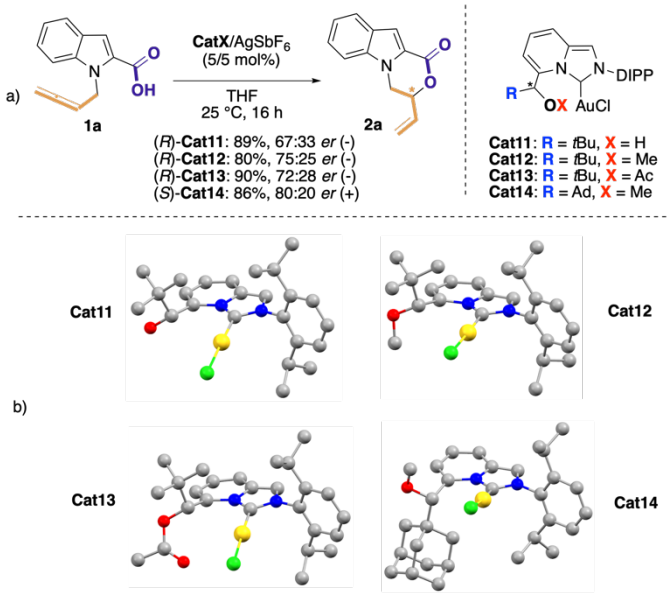


Figure 4. New chiral ImPyAuCl complexes for the enantioselective synthesis of the 3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indol-1-ones **2a**.

The introduction of an enantiomerically pure secondary alcohol at the C(5)-site was addressed, enabling electronic as well as steric fine-tuning at the stereogenic centre.[15] In this direction, chiral ImPyAuCl complexes **Cat11–14** were prepared (87–99%) by considering *t*Bu and adamantyl substituents at the carbinol site and different oxygenated moieties *i.e.*, OH, OMe, and OAc groups at the alcoholic site. Firstly, structural insights were obtained from X-ray diffraction analysis (Figure 4). All the complexes **Cat11–14** showed orthogonal orientation of the alkyl substituent with respect to the ImPy plane (dihedral angle 92.36–94.04°) with no O–Au contacts. This general spatial arrangement minimizes steric congestions that would results alternative *pseudo*-eclipsed conformations. Moreover, a solvated molecule of THF engaging a strong H-bonding interaction with OH group (O_{THF}···H–O 1.864 Å) was localized in the **Cat11** unit cell.

Aiming at verifying the efficiency of the enantiomerically pure carbene complexes **Cat11–14** in the present enantioselective hydrocarboxylation of allenes, the corresponding *in situ* formed cationic Au(I) complexes (5 mol% of $AgSbF_6$) were tested in the ring-closure of **1a**. In all cases, very high isolated yields of **2a** were obtained at rt in THF and 16 h reaction time (80–90% yield). Interestingly, a marked effect of the carbinol group functionalization on the stereochemical outcome of the process was recorded. As a matter of fact, while (*R*)-**Cat11** featuring unprotected OH group afforded (+)-**2a** in 67:33 *er*, the corresponding methyl ether (*R*)-**Cat12** led to a significantly higher steroinduction (75:25 *er*). Similar behavior was also obtained using the OAc analogous (*R*)-**Cat13** (72:28 *er*

of (-)-**2a**). Finally, the employment of the 1-Ad containing complex (*S*)-**Cat14** led to a slight improvement in stereoselectivity, yielding (+)-**2a** in 80:20 *er*.

In summary, a new gold catalyzed intramolecular hydrocarboxylation of allenes is described as a direct synthetic route to densely functionalized 3,4-dihydro-[1,4]oxazinoindol-1-ones. Main advantages of the protocols rely on the readily availability of the starting material, the functional group tolerance and the mild reaction conditions. Fine-tunable NHC-ImPy ligands, featuring electronically modulable aryl units, afforded high yields (up to 98%) to be obtained together with high level of chemo- and regioselectivity. Preliminary attempts to describe an unprecedented enantioselective variant of the protocol were also undertaken by means of modulable ImPy complexes **Cat11–14**. Moderate level of enantiomeric control (up to 80:20 *er*) were documented.

Conflicts of interest

There are no conflicts to declare.

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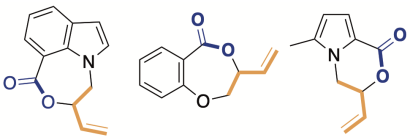
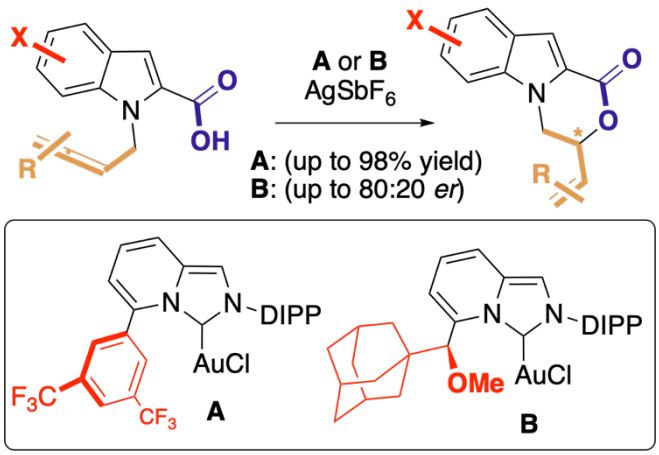


2k: 15% **2l**: 12% **2m**: 18%


X
O
OH
N
R
A or B
AgSbF6
A: (up to 98% yield)
B: (up to 80:20 er)
X
O
O
N
R
N
N
DIPP
AuCl
F3C
CF3
A
N
N
DIPP
OMe
AuCl
B