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

Riccardo Pedrazzani, [ab] Emanuele Pinosa,[ab] Giulio Bertuzzi,[ab] Magda Monari, *[ab] Samuel Lauzon, [c] Thierry Ollevier *[c] and Marco Bandini *[ab]

A new [Au(I)] catalyzed intramolecular hydrocarboxylation of allenes is presented as a valuable synthetic route to oxazino-indolones. The use 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 reaction conditions (r.t., 16 h), and (iii) high yields (up to 90%). Preliminary attempts towards an enantioselective version (81 : 19 er) are 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 an 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 progress in organic synthesis due to their wide presence in bioactive compounds and naturally occurring species, and as precursors of pharmacologically active ingredients (Fig. 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 lead to moderately functionalizable polycyclic-fused indolyl scaffolds (Fig. 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** (Fig. 1c).[6] This approach would lead to direct access to 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 can introduce some constraints 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)[7] catalysts, some of us have recently documented the high performance of the CF_3–aryl–ImPy-based gold complex **Cat1**

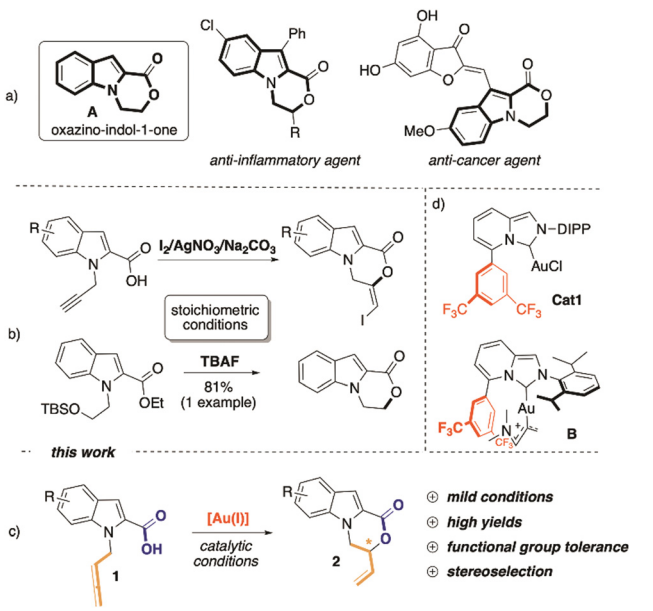

Fig. 1 (a) Examples of bioactive compounds based on the targeted oxazino-indol-1-one core **A**. (b) Stoichiometric synthetic routes towards oxazino-indol-1-ones – State of the art. (c) [Au(I)] catalyzed hydrocarboxylation of allenes.

[a] *Dipartimento di Chimica "Giacomo Ciamician", Alma Mater Studiorum – Università di Bologna, via Selmi 2, Bologna, 4016, Italy. E-mail: magda.monari@unibo.it, marco.bandini@unibo.it*
[b] *Center for Chemical Catalysis - C^3, Alma Mater Studiorum, via Selmi 2, Bologna, 4016, Italy*
[c] *Département de chimie, 1045 avenue de la Médecine, Université Laval, Québec, G1V 0A6, Qc, Canada. E-mail: Thierry.Ollevier@chm.ulaval.ca*

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in the electrophilic manipulation of several π-systems (Fig. 1d).[8] This peculiar catalytic activity was rationalized based on secondary interactions regarding the cationic alkenyl–[Au(I)]-type intermediates **B**.[9]

These findings, combined with our recent interest towards [Au(I)] assisted synthesis of polycyclic fused indolyl cores,[10] prompted us to verify the efficiency of **Cat1** in the model hydrocarboxylation reaction of **1a** (Fig. 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,[11] [Au(I)] catalyzed hydrocarboxylations of cumulenes have faced far less success in the literature with applications merely related to the preparation of γ-butyrolactones.[12]

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[13] nitrogen heterocyclic carbenes (NHCs),[14] comprising diverse substitutions at the C(5)-position was considered (Fig. 2a). In this context, besides the already documented gold complexes **Cat1,5,6**, three new dimethyl amino-based ImPy scaffolds were targeted (**Cat2–4**) 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 [Me_2SAuCl] and K_2CO_3 in acetone.[15] Furthermore, the new complexes **Cat2–4** were fully characterized also *via* X-ray diffraction and the resulting molecular structures are reported in Fig. 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**.[8] These two pre-catalysts with electron-rich functionalization displayed longer arene···Au *vs.* **Cat6** contact (3.352 Å) and a shortening of the distance was observed for *meta*-substituted arenes *vs. para*-ones (3.623 Å *vs.* 3.566 Å). Furthermore, both –NMe_2 groups have a high degree of planarity, due to the conjugation with the phenyl ring (see ESI†). 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) (see ESI†, Table S1).

Delightfully, **Cat1** (5 mol%) exhibited 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, r.t. entry 1 Table 1). 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–ImPy(Au)Cl complex **Cat6** that produced **2a** in a lower amount (72% yield, entry 6).

Interestingly, the family of ImPyAuCl catalysts proved more competent 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 was 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 trace amounts, 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 the absence of an Ag salt (entry 14) and an Au(I) complex (entry 15), resulting in no

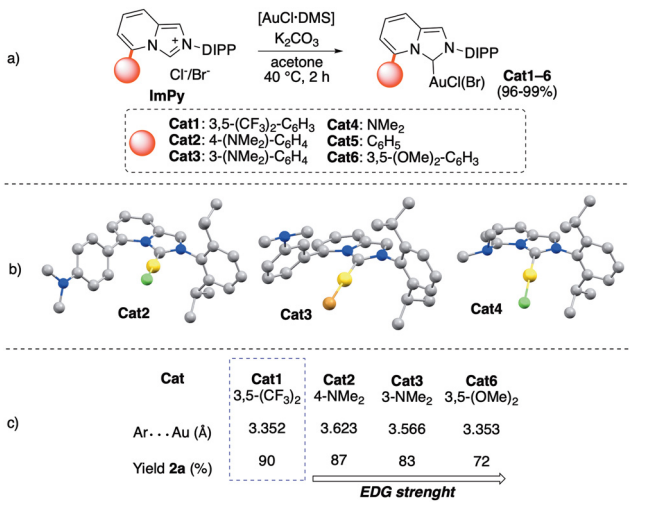
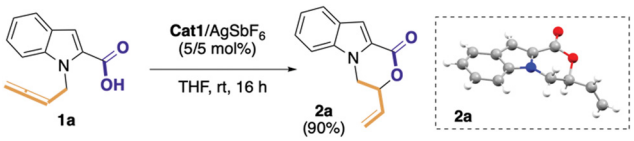


Fig. 2 (a) Collection of C(5)-functionalized ImPyAuCl/Br complexes used in this study. (b) Single crystal X-ray structures of complexes **Cat2–4**. (c) Ar···Au distance/catalytic performance correlation for C(5)-aryl substituted ImPy–Au complexes (DIPP: diisopropylaniline).

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** (iPrAuCl)	69
8	**Cat8** (PPh_3AuCl)	42
9	**Cat9** (JohnPhosAuCl)	<5
10[c]	**Cat10** ($picAuCl_2$)	<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 r.t. [b] Determined after flash chromatography as an average of two runs. [c] Using 10 mol% of $AgSbF_6$. NR: no reaction. $picAuCl_2$: dichloro(2-pyridinecarboxylato)gold.

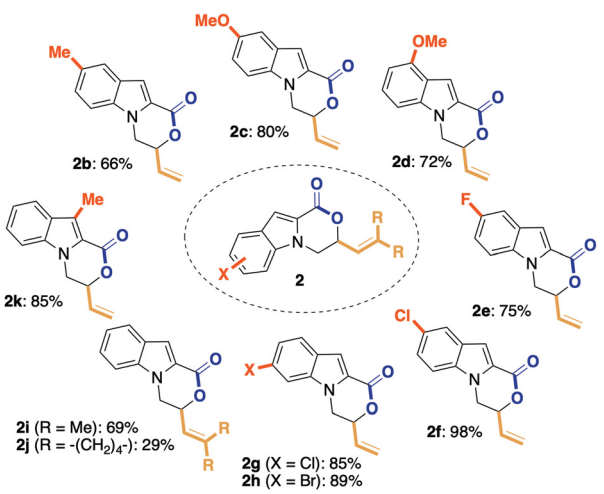
conversion in both cases. Finally, other parameters, such as a gold counterion and reaction media, were investigated but no improvements with respect to the optimal conditions were recorded (entries 11–18). The catalytic performance of the C(5)-aryl-containing complexes **Cat1–3** and **Cat6** was analysed in comparison with the relative Ar···Au distances recorded in the solid state (Fig. 2c). Interestingly, in the small series of electron-rich arene containing species (*i.e.*, **Cat2,3** and **Cat6**) a shortening of the arene/metal contact directly related to the strengths of the EDGs is observed, with the *meta* substitution predominating over the *para*-ones (see **Cat2** *vs.* **Cat3**). In particular, stronger 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 sped up the ring-closing event resulting in 90% isolated yield of **2a**.

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 the optimal C–O ring-closure conditions (Scheme 1, see ESI† for synthetic details). Remarkably, electron-donating groups (Me and OMe) could be conveniently accommodated both at the C(3), C(4) and C(5) positions of the benzenoid ring by providing the desired compounds **2b–d,k** in good to excellent yields (66–85%). 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%). 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 a synthetically useful 69% yield.

On the other hand, the procedure also faced some limitations in substrate scope. As a matter of fact, attempts to extend the process to differently structured seven-membered rings (**2l,m**) or pyrrolyl-2-carboxylic acid **1n** resulted in modest conversions (*ca.* 12–18% yield).[16]

Based on these promising results, we then turned our attention towards the development of an unprecedented 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.

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.[17] 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 (Fig. 3). All the complexes **Cat11–14** showed orthogonal orientation of the alkyl substituent with respect to the ImPy plane (dihedral angle range 92.36–94.04°) with no O···Au contacts. This general spatial arrangement minimizes steric congestions that would result in alternative *pseudo*-eclipsed conformations. Moreover, a solvated molecule of THF engaging a strong H-bonding interaction with the 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 r.t. in THF and 16 h reaction time (80–90% yield). Interestingly, a marked effect of the carbinol functionalization on the stereochemical outcome of the process was recorded. As a matter of



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

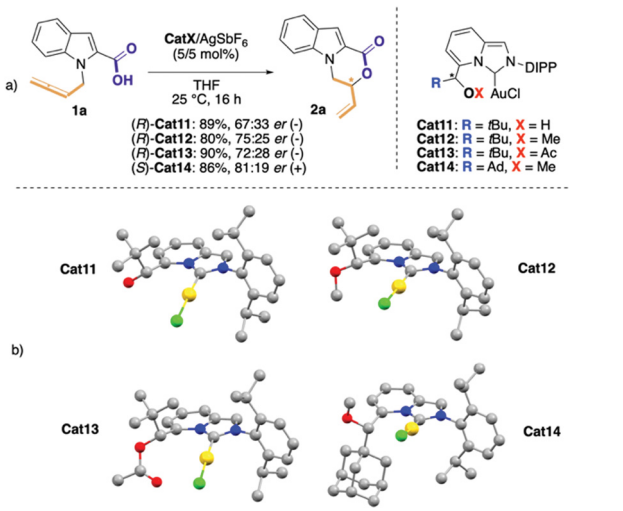


Fig. 3 New chiral ImPyAuCl complexes for the enantioselective synthesis of the 3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indol-1-ones **2a**. (a) Chemical/stereochemical outomes; (b) X-ray structures.

fact, while (*R*)-**Cat11** featuring an unprotected OH group afforded (−)-**2a** in 67 : 33 er, the corresponding methyl ether (*R*)-**Cat12** led to a significantly higher stereoinduction (75 : 25 er). Similar behaviour 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 81 : 19 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. The main advantages of the protocol rely on the ready 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 a high level of chemo- and regioselectivity. Preliminary attempts towards an unprecedented enantioselective variant of the protocol were also undertaken by means of modulable ImPy complexes **Cat11–14**. A moderate level of enantiomeric control (up to 81 : 19 er) was documented.

Conflicts of interest

There are no conflicts to declare.

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