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Communication

Regiocontrolled gold(I)-catalyzed cyclization reactions of *N*-(3-iodoprop-2-ynyl)-*N*-tosylanilines

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Dedicated to the memory of the late professor José M. Concellón

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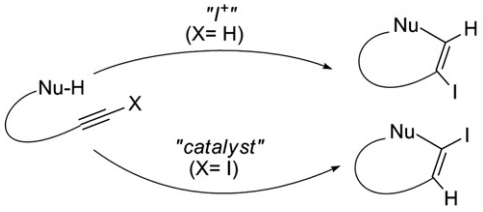
ABSTRACT

The gold(I)-catalyzed cyclization reactions of *N*-(3-Iodoprop-2-ynyl)-*N*-tosylaniline derivatives afford iodinated 1,2-dihydroquinoline derivatives. Two regioisomer products are obtained, one derived from direct cyclization and other involving concomitant 1,2-iodo migration. The ratio of these two products can be modulated by a proper ancillary ligand in the gold catalyst.

1. Introduction

The addition of arenes across alkynes is a powerful transformation for developing C–C bond-making processes. Its intramolecular version offers a conceptually attractive entry into a straightforward assembly of a variety of benzofused skeletons. Thus, mechanistically diverse metal-catalyzed reactions [1] and even Brønsted or Lewis acid-catalyzed transformations [2] have been reported. Notably, connected alkyne activation processes triggered upon the addition of stoichiometric amounts of a proper iodonium donor represent a versatile and complementary strategy to selectively access to related arylated products [3]. Furthermore, current awareness of the potential of gold-catalyzed organic transformations has a major impact in the advance of the topic [4].

On the other hand, cross-coupling reactions of synthetic building-blocks based on Csp^2-I bonds are well established synthetic tools associated with contemporary strategies oriented towards the rapid molecular diversification of a given core. All this considered, there is a need for advances in fundamental methodology aimed at an efficient and selective assembly of key iodinated frames. For this purpose, besides site-selective iodinations, two alternatives based on *de novo* elaboration strategies can be envisaged, as outlined (Eq. (1)). Iodination events that involve concomitant cyclization or the use of pre-iodinated building blocks for the elaboration of the target core, preferably via catalytic processes, are useful choices [5].



(1)

The potential of iodine to undergo 1,2-migration in metal-catalyzed cyclizations involving 1-iodo-1-alkynes [6], and a seminal remark by Fürstner and coworkers on the control of the regioselectivity in cyclization reactions leading to halophenanthrene derivatives as a function of the metal catalyst used (Eq. (2)) [7], provide ground to explore the possibility of achieving related product modulation by an alternative and appropriate ligand tuning in gold(I)-catalyzed carbocyclization reactions leading to heterocyclic scaffolds.

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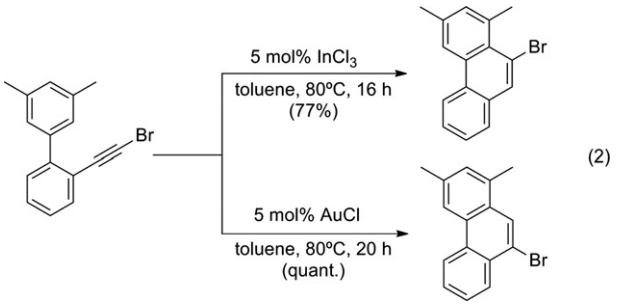


(2)

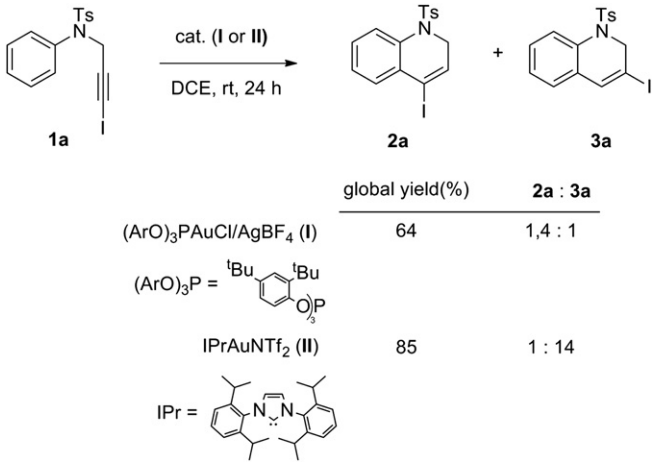
Now, we disclose preliminary results on the feasibility of such an expectation.

2. Results and discussion

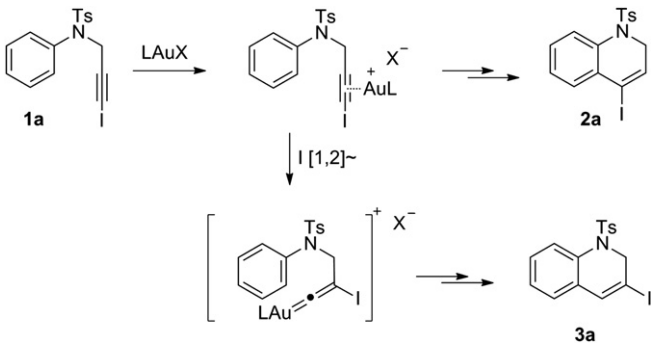
On the ground of all of the above discussed and keeping in mind the inherent interest associated with the so-called privileged structures in medicinal chemistry [8] we choose *N*-(3-iodoprop-2-ynyl)-*N*-tosylaniline as a useful model compound. In terms of the catalyst, chloride and bis(trifluoromethanesulfonyl)imidate (NTf_2) gold(I) complexes were selected. As Gagosz recognized, the latter counter anion behaves similar to other weakly coordinating anions and does not require the addition of a silver (I) salt to render an electrophilic gold centre [9]. Concerning the selection of the ligand intended to be responsible for the control of the selectivity, and considering the multiple options existent, this work is focused on the investigation of the reactivity of two limit systems to try to access cationic gold centres with significantly differentiated electron density [10]. Specifically, attention was paid to gold complexes derived from either the bulky tris(2,4-di-*tert*-butylphenyl)phosphite and the *N*-heterocyclic carbene ligand IPr [IPr: 1,3-bis(2,6-diisopropyl)phenylimidazol-2-ylidene] [11].

In the initial trials [12], the transformations were performed under argon atmosphere, at room temperature (c.a. 20 °C) for a period of 24 h. The reactions were conducted using 0.3 mmol of the starting alkyne (0.15 M solutions in dichloroethane), and the load of the catalytic system $(ArO)_3PAuCl/AgBF_4$ (1:1 ratio) (**I**) or $IPrAuNTf_2$ (**II**) was kept at 3 mol.

The aniline derivative **1a** was exposed to both catalytic systems and the main findings are depicted in Scheme 1.



Scheme 1. Exploratory trial proving the ligand influence over a gold(I)-catalyzed cyclization of *N*-(3-iodoprop-2-ynyl)-*N*-tosylaniline **1a**.

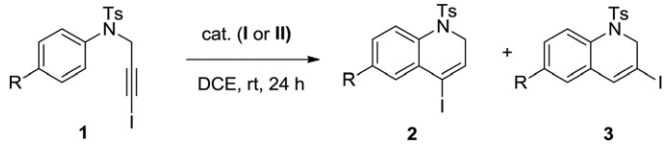


Scheme 2. Proposed rationalization for the observed manifold of cycloisomerization products in gold(I)-catalyzed cyclizations of *N*-(3-iodoprop-2-ynyl)-*N*-tosylaniline **1a**.

The outcome of these experiments provides support to the hypothesis of affecting the product distribution in gold (I)-catalyzed hydroarylation reactions involving iodoalkynes by ligand tuning. The direct cyclization is favoured by the use of the phosphite ligand that would drive the classic cyclization as a result of the electrophilic nature of the gold centre, resulting in the formation of the cyclization product **2a**. On the contrary, the catalyst based on IPr ligand, that is strong donor to the metal, comparatively favours the 1,2-iodine shift that would switch the nature of the intermediate to a vinylidine species that, eventually, would render product **3a**. For a tentative draft that justify the formation of the observed 1,2-dihydroquinoline derivatives in a graphical manner, see Scheme 2. Their structures were drawn on the basis of detailed nmr spectroscopic studies. Also, the structure of **3a** was unambiguously confirmed by X-ray diffraction analysis [13].

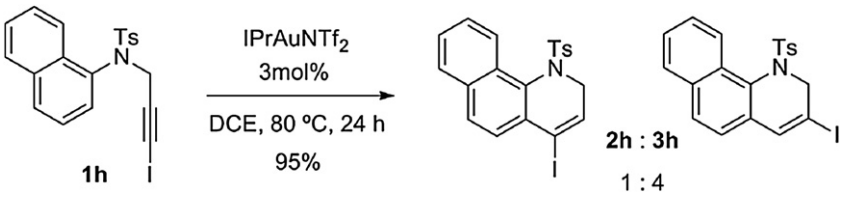
The metal-control over product distribution early documented for the elaboration of halophenanthrenes [7] implicates substrates in which the arylating ring is an electron-rich one that, in general, has been considered a requirement for gold-catalyzed cyclizations involving hydroarylation reactions. For this reason, it would be of interest to begin the exploration of the versatility and constrains associated with the cyclization now being reported. Importantly, it could be reasonably anticipated that the nature of the substituents of the arene ring would also play a key role to determine the nature of the cyclization mixture. So, research to broach the efficiency and the subtleness behind this process were conducted and the most relevant results are now presented (Table 1).

Table 1



Entry	Substrate **1**	Catalyst[a]	Global yield[b] (%)	Ratio[c] **2**:**3**
1	**1b** (R: Me)	**I**	(98)	7.9:1
2	**1b** (R: Me)	**II**	75 (99)	1:4.8
3	**1c** (R: OMe)	**II**	81	1:1.5
4	**1d** (R: I)	**II**	52	1:70
5	**1e** (R: Cl)[d]	**I**	79	1:2.2
6	**1e** (R: Cl)	**II**	80	<1:99<
7	**1f** (R: NO_2)[d]	**II**	–	
8	**1g** (R: COMe)	**I**	67	3.5:1
9	**1g** (R: COMe)	**II**	72	1:23

[a] For the catalyst structure, see Scheme 1.
[b] Isolated yields; within brackets, yields estimated by nmr.
[c] Calculated by nmr.
[d] The reactions were carried out at 80 °C.



Scheme 3. IPrAuNTf$_2$-catalyzed cyclization of *N*-(3-iodoprop-2-ynyl)-*N*-tosyl-1-naphthylamine derivative **1h**.

The data in Table 1 clearly evidence a modulation of the nature of the reaction products by both, the ancillary ligand on the catalytic system and the substituent onto the substrate that becomes part of the metal systems upon coordination. Again, for a given substrate **1**, catalyst **II** gives always lower **2**:**3** ratios, favouring the formation of the corresponding cyclization product **3** arising from a 1,2-iodine shift (entries 1/2; 5/6 and 8/9). An additional experiment was conducted to scrutinize the possibility of a major counterion effect also operating [14]. Thus, **1b** was also subjected to reaction with the alternative catalytic system resulting from the $AgBF_4$ activation of the IPrAuCl complex. When **1b** was exposed, under argon atmosphere, to 3 mol% of this catalytic system, in DCE at room temperature for 21 h, complete consumption of the starting iodoalkyne and the formation of a 1:5 ratio of **2b**:**3b** in 99% overall yield was noticed (calculated by nmr using 1,3,5-trimethoxybenzene as inner reference). The outcome of this experiment is in line with the previous result obtained using IPrAuNTf$_2$ as catalyst and suggests that for this transformation, the counterion is not significantly affecting the observed product distribution.

On the other hand, the use of a substrate **1** having a more electron-rich arene speeds comparatively the direct cyclization leading to **2**, thus hampering the formation of product **3** derived from a preorganization of the system via 1,2-migration [15]. So, for instance, using the catalyst **II,** the relative amount of compound **3** diminished in going from simple phenyl to 4-methoxyphenyl, with an intermediate figure for the tolyl derivative (see Scheme 2 and Table 1 entries 3 and 2, respectively). Significantly, this process is also compatible with the presence of moderately deactivating groups though, so far, the cyclization is inhibited when a strong-deactivating nitro group is present. Regarding the selectivity, the presence of electron-withdrawing groups should slow the direct cyclization process, allowing for the iodine migration to occur. In fact, excellent selectivity in favour of the formation of the corresponding product **3** was noticed in those cases (see entries 4, 6 and 9).

Moreover, for substrate **1b** the reactivity of gold (I) catalysts bearing some phosphine as ligand was also investigated. As a function of its electronic characteristics, this class of ligand is expected to show behaviour in-between the phosphite and the NHC-type ligands. Gratifyingly, in good agreement with this assumption, this turns out to be the case. Thus, the use of PPh_3 resulted in the formation of a 1.2:1 ratio of **2b**:**3b** in 81% overall yield, while it switches to 1:1.7, global yield (calculated by nmr using 1,3,5-trimethoxybenzene as inner reference) of 97%, using di-*tert*-butyl(*o*-biphenyl)phosphine [P(*t*-Bu)$_2$(*o*-biphenyl), JOHNPHOS].

Finally, the reaction of a 2-naphthyl derivative was investigated to check the consistency of the underlying regiocontrol noticed for aniline derivatives, as well to test a plausible selectivity issue concerning the ring becoming involved in the cyclization event. The main findings are graphically summarized in Scheme 3.

In this case a more sluggish process occurs, likely due to conformational constrains imposed by the interaction of the bulky tosyl and naphthyl appendages onto nitrogen to enable the cyclization. Nevertheless, simply increasing the reaction temperature resulted in an efficient and selective transformation, with just cyclization at one ring taking place and, interestingly, again the use of the IPr ligand affords predominantly the cyclization product incorporating the iodine migration in the structure of the major isomer.

Further work devoted to improve the efficiency, scope and some practical issues concerning the synthetic potential of the herein sketched new transformation are in progress. Among them are research efforts addressing solvent and temperature effects and other factors that might affect the selectivity. Also further ligand optimization studies and work aimed at the eventual implementation of this chemistry to prepare other hetero and carbocycles in a related manner will be undertaken.

3. Conclusions

In short, initial exploratory studies and conceptual basis for a new protocol to access differently site-iodinated relevant heterocyclic frames are reported. This product diversity is accessed by judicious ligand tuning in gold (I)-catalyzed intramolecular hydroarylation reactions involving simple tethered iodoalkynyl and arene partners.

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Appendix. Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.jorganchem.2010.09.014.

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