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Gold(I)-catalysed transformations of heterocycle derived 1,3-enynes

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Background

Following our interest in the chemistry of lactam and lactone derived triflates and phosphates as key intermediates in the synthesis of natural compounds, we have previously demonstrated that the gold(I)-catalysed reaction N-Boc protected 6alkynyl-3,4-dihydro-2*H*-pyridines affords synthetically useful vinylogous amides (β-enaminones). The reaction has been studied in detail in order to optimize the reaction conditions, enlarge the scope and have insights into the mechanism and the structural features that selectively favor the 6-endo-dig oxyauration of the triple bond.¹ Inspired by these results and by our general interest on the synthesis of heterocycle derived natural compounds, we envisioned that when the N-protecting group is a *p*-toluenesulfonyl (Ts) the intramolecular path is prevented.



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Reaction conditions: i. Ph₃PAuOTf (3 mol%), toluene, 110 °C; ii. KOH (6 eq), t-BuOH, 85 °C



With the aim of extending the methodology to N-Tosyl- and O- heterocycles, we turned our attention to an intermolecular oxidative path involving the use of nucleophilic oxidants (Y⁺-O⁻) such as pyiridine or quinoline N-oxides.² The mechanism is supposed to go through an α -oxo gold carbenic intermediate I, which undergoes rapid 1,2-CH insertion, eventually affording the divinyl ketone 2, in which one of the double bonds is embedded in the heterocycle. These structures are widely represented in natural products and additionally they can be easily converted into polycyclic compounds under feasible electrocyclic Nazarov reaction.

The envne substrates 1 were prepared by Sonogashira coupling between a lactam or lactone derived triflate and a terminal alkyne. Variability was introduced both on the heterocyclic ring in terms of heteroatom (oxygen or protected nitrogen) and size (6 or 7 member), and on the alkyne side chain.





5% Ph₃PAuCl,



product 2 were obtained with six-membered lactam derived enynes. Caprolactam and lactone derived enynes showed a higher amount of overoxidation products **3**. It appears that both steric and electronic effects are involved in determining the regioselectivity of the reaction.

> LAu^+ overoxidation 'n



Table 1. Optimization of the reaction conditions.

^{*a*} All the reactions were performed with LAuCl (5 mol%) and AgX (5 mol%) in toluene at 110 °C if not otherwise specified. ^b 1.2 equiv., DCE, rt. ^c 2.0 equiv., DCE, 70 °C. ^d rt. ^e 5.0 equiv. of oxidant in the presence of only AgNTf₂. ^{*f*} 15% of catalyst.

What happens when no adjacent CH_2 groups are present?

With the aim of bringing evidence to the involvement of a gold carbene intermediate in the reaction mechanism we synthesized enyne **1**g, in which the 1,2-CH insertion path is precluded at all, and we let it react in the presence of *cis*-stilbene as a carbene trap. However, we did not recover any cyclopropanation product but only compound **2g** alongside with the diketone **3g** in 4:1 ratio.



We speculated that compound **2g** can arise from a deprotonative Grob-type fragmentation of III, followed by fast protodeauration of IV, the driving force of the process being the formation of a highly conjugated compound.⁴

New synthetic approach to Strigolactones analogues



Ongoing research

We are currently working on the intramolecular cyclization of heterocycle derived enynes bearing a substituent on the 3- position of the ring. This substituent could act as an internal nucleophile and attack the gold-activated triple bond, thus opening the access to more complex structures.



¹ A. Oppedisano, C. Prandi, P. Venturello, A. Deagostino, G. Goti, D. Scarpi, E. G. Occhiato, J. Org. Chem. **2013**, 78, 11007-11016; D. Scarpi, S. Begliomini, C. Prandi, A. Oppedisano, A. Deagostino, E. Gómez-Bengoa, B. Fiser, E. G. Occhiato, Eur. J. Org. Chem. 2015, 15, 3251-3265. ² L. Zhang, Acc. Chem. Res. **2014**, 47, 3, 877-888; Z. Zheng, Z. Wang, Y. Wang, L. Zhang, Chem. Soc. Rev. **2016**, 45, 4448-4458. ³ B. Lu, C. Li, L. Zhang, J. Am. Chem. Soc. **2010**, 132, 14070-14072.

⁴ Y. Wang, A. Genoux, S. Ghorai, H. Chen, R. Todd, L. Zhang, *Adv. Synth. Catal.* **2016**, *358*, 1417-1420.

⁵ C. Bhattacharya, P. Bonfante, A. Deagostino, Y. Kapulnik, P. Larini, E. G. Occhiato, C. Prandi, P. Venturello, Org. Biomol. Chem. 2009, 7, 3413-3420; C. Prandi, E. G. Occhiato, S. Tabasso, P. Bonfante, M. Novero, D. Scarpi, M. E. Bova, I. Miletto, Eur. J. Org. Chem. 2011, 3781-3793

We envisaged that the gold-catalysed oxidation, followed by Nazarov electrocyclization, could be exploited to access indolyl analogues of Strigolactones, a class of plant hormones known for their effects on plants and as antitumoral agents. The herein proposed sequence allows the introduction of suitable substituents in the β -position of the cyclopentaindolylone nucleus.

