Journal of Organometallic Chemistry xxx (2015) 1–5

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Facile and efficient synthesis of [1,4]oxazino[3,2-*b*]indoles and 1*H*-pyrazino[2,3-*b*]indoles through gold-catalyzed cascade cyclization of (azido)ynamides

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ARTICLE INFO

Article history:
Received 31 December 2014
Received in revised form
30 January 2015
Accepted 31 January 2015
Available online xxx

Keywords:
Gold
Heterocycles
Homogeneous catalysis
Synthetic methods

ABSTRACT

[1,4]Oxazino[3,2-*b*]indoles as well as 1*H*-pyrazino[2,3-*b*]indoles are constructed in good to excellent yields via gold-catalyzed cascade cyclization of (azido)ynamides. The use of readily available starting materials, a simple procedure and mild reaction conditions are other significant features of this method.

Introduction

Indoles are among the most widely distributed heterocyclic compounds in nature and are common structural motifs in many pharmaceuticals and bioactive molecules [1]. Although numerous strategies for indole synthesis have been developed, access to the [1,4]oxazino[3,2-*b*]indoles or 1*H*-pyrazino[2,3-*b*]indoles remains scarce [2]. Consequently, the development of novel methods for the construction of these skeletons is highly desirable, especially those based on assembling structures directly from readily available and easily diversified building blocks. Catalytic transformations involving gold carbenes are arguably the most important aspect of homogeneous gold catalysis due to their versatile reactivities [3]. Recently, gold-catalyzed intramolecular or intermolecular alkyne oxidations by N–O bond oxidants have become an expedient way to generate the synthetically versatile α-oxo gold carbenes, and various efficient synthetic methods have been developed based on this strategy [4,5]. For accessing the related α-imino gold carbenes, however, only limited success has been achieved by the intramolecular reaction of alkyne and azide [6,7]. In 2005, Toste and his co-workers used azide as an effective nitrene equivalent and realized the first protocol for the generation of α-imino gold carbine [6a]. Later, elegant studies about the synthesis of indoles from alkynyl azides were demonstrated by Gagosz [6b] and Zhang [6c], independently. Despite the significance of these transformations, it is still highly desirable to explore new reactions based on such a gold-catalyzed generation of α-imino gold carbenes from alkynes, which is more atom-economic than the related oxidation approach.

Inspired by these results and our recent findings on the gold-catalyzed tandem reactions based on ynamides [8,9], we envisioned that the synthesis of [1,4]oxazino[3,2-*b*]indoles or 1*H*-pyrazino[2,3-*b*]indoles might be achieved from ynamide substrate **1** through a gold-catalyzed tandem intramolecular alkyne amination/X–H insertion (Scheme 1). Herein, we would like to describe the realization of such a gold-catalyzed tandem transformations of (azido)ynamides,

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http://dx.doi.org/10.1016/j.jorganchem.2015.01.029
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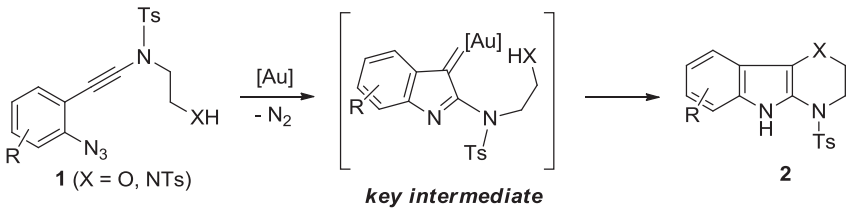


Scheme 1. Initial design.

affording the corresponding [1,4]oxazino[3,2-*b*]indoles and 1*H*-pyrazino[2,3-*b*]indole in good to excellent yields.

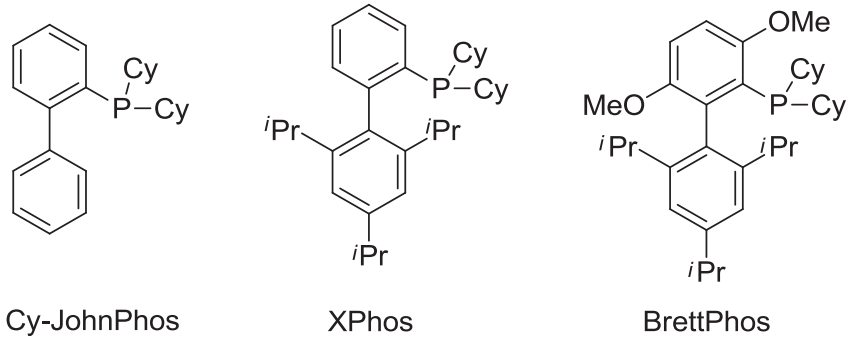
Results and discussion

We began our studies by choosing **1a** as the model substrate to examine the reaction and selected results are summarized in Table 1. The influence of various gold catalysts bearing different phosphine ligands was first screened (Table 1, entries 1–6). Pleasingly, all the gold catalysts, such as [$Ph_3PAuNTf_2$, $IPrAuNTf_2$, $(4\text{-}CF_3C_6H_4)_3PAuNTf_2$, Cy-JohnPhosAuNTf$_2$, XPhosAuNTf$_2$ and BrettPhosAuNTf$_2$], did promote this transformation, leading to the target compound **2a** in good to excellent yields, and XPhosAuNTf$_2$ was best suited for this reaction to afford **2a** in 91% yield (Table 1, entry 5). Importantly, no background oxazolidine formation via a gold-catalyzed 5-*exo*-*dig* cyclization was observed in all cases. Of note, non-noble metals such as $Zn(OTf)_2$ and $Cu(OTf)_2$ cannot catalyze such a cascade cyclization and only hydration product was isolated as the main product (Table 1, entries 7 and 8). In addition, the use of other solvents such as THF and toluene led to a significantly decreased yield (Table 1, entries 9 and 10).

Finally, a plausible mechanism to rationalize the catalytic transformation is proposed, as depicted in Scheme 2. Taking substrate **1a** for example, the reaction probably starts with the coordination of the gold catalyst to the alkyne, which would then undergo the concomitant nucleophilic attack of the azide nitrogen to generate intermediate **A**. The gold-carbenoid intermediate **B** is expected to be formed at this stage via the release of molecular nitrogen. Target compound **2a** should thus be obtained via the intramolecular trapping of the α-imino gold carbenoid by the OH moiety and the subsequent aromatization/deauration.

Conclusions

In summary, we have developed a facile and efficient solution for the synthesis of [1,4]oxazino[3,2-b]indoles and 1*H*-pyrazino[2,3-*b*]indoles via a gold-catalyzed tandem transformations of (azido)ynamides. Importantly, in comparison with the related oxidation approach to the generation of gold carbenes [4,5], this strategy provides a more atom-economic way for the generation of gold carbenes. The use of readily available substrates, a simple procedure, and mild reaction conditions and, in particular, no need



With the optimal reaction conditions in hand (Table 1, entry 5), the scope of the transformation was then explored. As shown in Table 2, ynamide substrates **1** bearing electron-withdrawing or electron-donating substituents such as Cl, Br, Me and MeO on the phenyl ring were well compatible with this transformation, leading to the efficient formation of the corresponding products [1,4]oxazino[3,2-*b*]indoles in 89–93% yields (Table 2, entries 1–6). To further illustrate the validity of our current methodology, an experiment using **1g** as the substrate was also carried out. Gratifyingly, the expected product 1*H*-pyrazino[2,3-*b*]indole **2g** could also be obtained in 80% yield (Table 2, entry 7). Thus, this cascade cyclization provides a highly efficient and convenient route for the construction of six-membered heterocycle-fused indole derivatives, which may have applications in drug development and chemical biology.

to exclude moisture or air ("open flask") render these methods potentially useful in organic synthesis. Further investigations into the synthetic applications of the current reaction are in progress in our laboratory.

Experiment section

Gold-catalyzed cascade cyclization of (azido)ynamides to [1,4] oxazino[3,2-b]indoles

XPhosAuNTf$_2$ (14.3 mg, 0.015 mmol) was added to a solution of the ynamide **1** (0.30 mmol) in DCE (6.0 mL) at room temperature. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. The reaction typically took 6 h. Upon completion, the mixture was then

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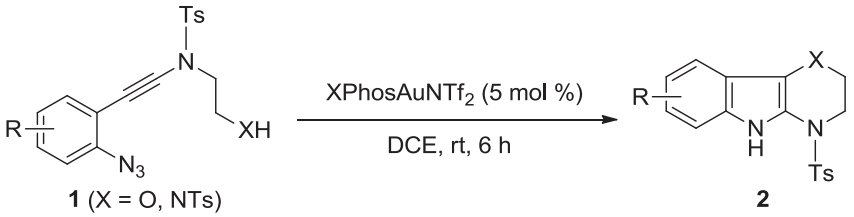
Table 1
Optimization of reaction conditions.[a]

1a **2a**

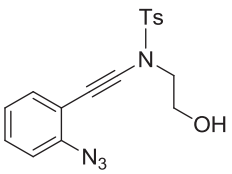
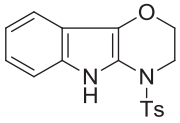
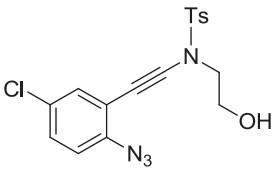
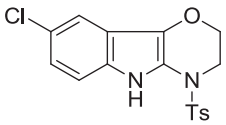
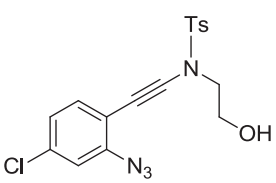
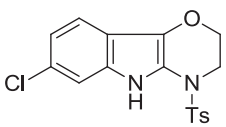
Entry	Metal catalyst	Solvent	Yield[b] (%)
1	$Ph_3PAuNTf_2$	DCE	82
2	$IPrAuNTf_2$	DCE	83
3	$(4\text{-}CF_3C_6H_4)_3PAuNTf_2$	DCE	82
4	Cy-JohnPhosAuNTf$_2$	DCE	89
5	XPhosAuNTf$_2$	DCE	91
6	BrettPhosAuNTf$_2$	DCE	85
7[c]	$Zn(OTf)_2$	DCE	<5
8[c]	$Cu(OTf)_2$	DCE	<5
9	BrettPhosAuNTf$_2$	THF	71
10	BrettPhosAuNTf$_2$	Toluene	79

[a] Reaction conditions: [**1a**] = 0.05 M; DCE: 1, 2-dichloroethane.
[b] Measured by ^{1}H NMR using diethyl phthalate as the internal standard.
[c] 2-(2-Azidophenyl)-*N*-(2-hydroxyethyl)-*N*-tosylacetamide was isolated as the main product.

Table 2
Reaction scope study.[a]

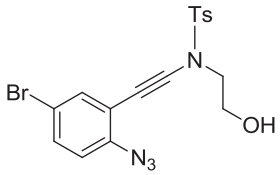
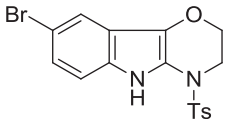
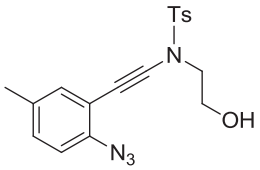
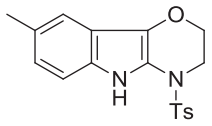
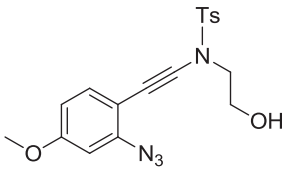
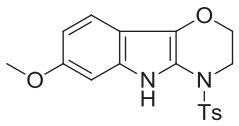
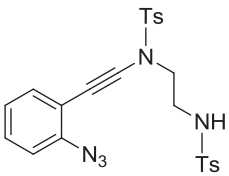
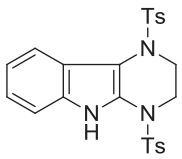


1 (X = O, NTs) **2**

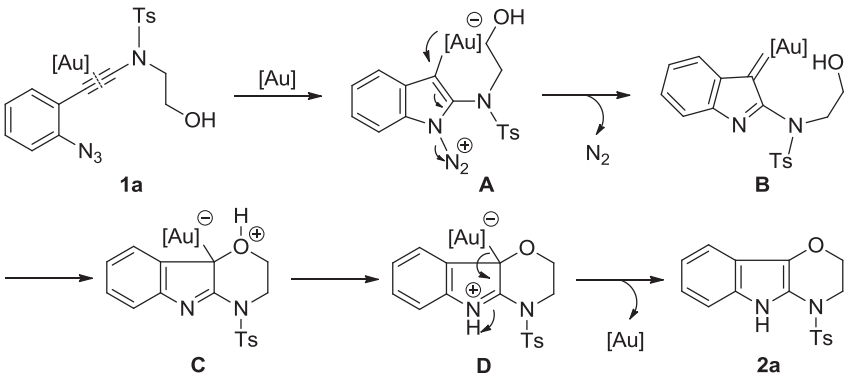
Entry	Substrate	**1**	Product	**2**	Yield [%]
1		**1a**		**2a**	90
2		**1b**		**2b**	92
3		**1c**		**2c**	90

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	1	Product	2	Yield [%]
4		**1d**		**2d**	93
5		**1e**		**2e**	91
6		**1f**		**2f**	89
7		**1g**		**2g**	80

[a] Reactions were run in vials; isolated yields are reported.



Scheme 2. Proposed reaction mechanism.

concentrated and the residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the desired product **2**.

Acknowledgments

We are grateful for the financial support from the National Natural Science Foundation of China (No. 21102119, 21272191 and 21302048), the Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT) and NFFTBS (No. J1310024).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2015.01.029.

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