Journal of Organometallic Chemistry 694 (2009) 515–519

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

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

Gold(I)-catalyzed [4+2] cycloaddition of *N*-(hex-5-enynyl) *tert*-butyloxycarbamates

Andrea Buzas [a], Florin Istrate [a], Xavier F. Le Goff [b], Yann Odabachian [a], Fabien Gagosz [a,*]

[a] Laboratoire Syntheses Organiques, Ecole Polytechnique, CNRS, Route de Scaclay, F-91128 Palaiseau Cedex, France
[b] Laboratoire Heteroelements et Coordination, Ecole Polytechnique, CNRS, F-91128 Palaiseau Cedex, France

ARTICLE INFO

Article history:
Received 17 June 2008
Received in revised form 31 October 2008
Accepted 3 November 2008
Available online 7 November 2008

Keywords:
Homogeneous catalysis
Gold complexes
Cycloaddition
Ynamides

ABSTRACT

A study concerning the gold(I)-catalyzed transformation of *N*-(hex-5-enynyl) *tert*-butyloxycarbamates is described. The mild conditions employed allow the moderately efficient but stereoselective synthesis of a range of bicyclic carbamates following a formal [4+2] cycloaddition process.

1. Introduction

During the past ten years, numerous organic synthetic chemists have become attracted to the chemistry of electron-deficient ynamines and ynamides. Such an interest may be explained by the fact that these reactive species are easily accessible and possess a high synthetic potential [1]. As a consequence, a wide variety of methodologies have been developed involving ynamines, and ynamides, and leading to the formation of a plethora of cyclic and acyclic nitrogen containing structures. Among these transformations, those using a metallic species as a catalyst remain predominant since they allow a rapid increase in structural complexity while working under generally mild reaction conditions. For instance various cyclizations or [2+2], [4+2], [2+2+2] annelation reactions have been described using Ru(II), Rh(I), Pt(II) or Pt(IV) based catalysts [2]. Electron-deficient ynamides have also proved to be suitable partners in a range of Pd(0)-catalyzed cross-coupling reactions [3] or in RCM transformations [4].

The ongoing interest in gold catalysis [5] has also led to the development of a few new transformations involving electron-deficient ynamides. The first study in this domain was made by Cossy and coworkers who described the gold(I)-catalyzed cycloisomerization of ene-ynamides into 2-azabicylco[3.1.0]hexanes [6]. Later on, the group of Hashmi [7] and our group [8] independently reported that *N*-alkynyl *tert*-butyloxycarbamates **1** could be converted in the presence of a gold(I) complex into a range of functionalized oxazolones **2** (Scheme 1). More recently, Hashmi and coworkers reported the elegant synthesis of dihydroindole and tetrahydroquinoline derivatives using electron-deficient ynamides as the substrates [9].

Following this recent success in the chemistry of ynamides, we envisaged to take advantage of this functionality to develop some other new gold mediated transformations. We were particularly keen to examine the cyclization of *N*-hex-5-enynyl *tert*-butyloxycarbamates **3** into bicyclic compounds **4** (Scheme 2). This transformation could be a synthetically useful extension of one of our previously reported transformations concerning the alkoxycylisation of 1,5-enynes [10].

We indeed recently reported that enynes of type **5** could be cyclized in the presence of an oxygen-containing nucleophile to stereoselectively furnish cyclopentenes **7** (Scheme 3, Eq. (1)).

This transformation is proposed to involve the formation of an intermediate **6** which is regio- and stereoselectively trapped by an *external* nucleophile. Intermediate **6** would possess a pronounced carbocationic character [11] and should be better depicted as a gold-stabilized homoallylic carbocation **6c** rather than cyclopropyl gold carbene **6a** [12]. By analogy with this transformation, we surmised that substrates of type **3** possessing an ynamide functionality could react in the presence of a gold(I) complex to generate an analogous intermediate of type **8** (Scheme 3, Eq. (2)). The *tert*-butyloxycarbonate moiety could perhaps play the role of an *internal* nucleophile to stereoselectively trap this intermediate. This would lead to the formation of the bicyclic compound 4 in which the stereochemistry of one of the new stereocentres would have been inverted by comparison with the previously reported transformation. Moreover, the presence of the enamide functionality in the cyclized products would be particularly useful to implement further transformations such as reduction, hydration or oxidation.

* Corresponding author.
E-mail address: gagosz@dcso.polytechnique.fr (F. Gagosz).

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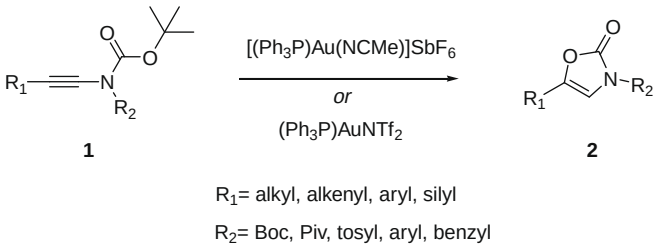
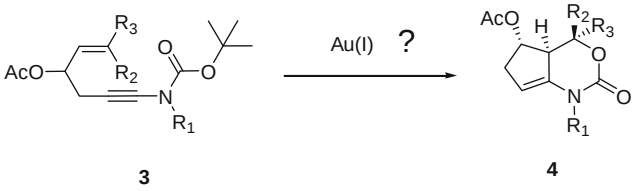
doi:10.1016/j.jorganchem.2008.11.004



Scheme 1. Cyclization of *N*-alkynyl *tert*-butyloxycarbamates.



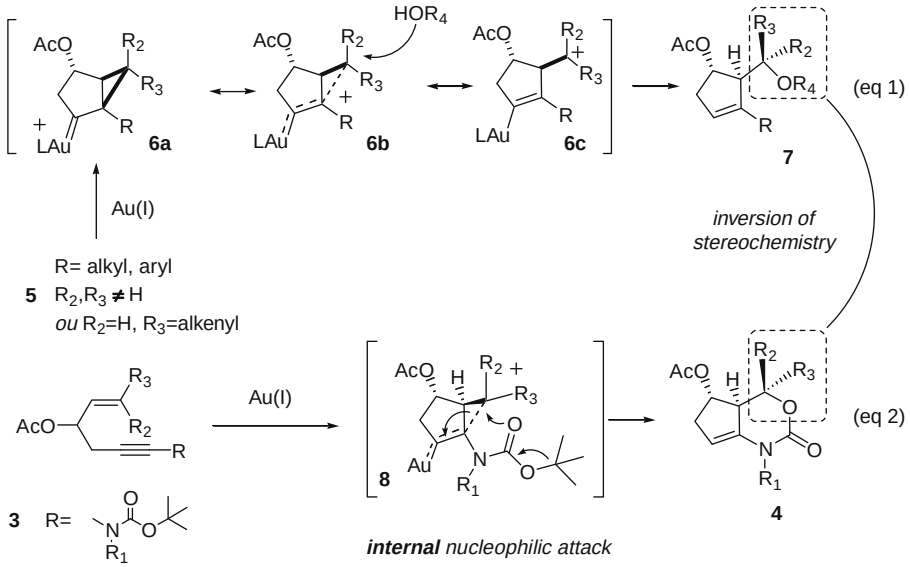
Scheme 2. Proposal of *N*-hex-5-enynyl *tert*-butyloxycarbamates cyclization.

2. Results and discussion

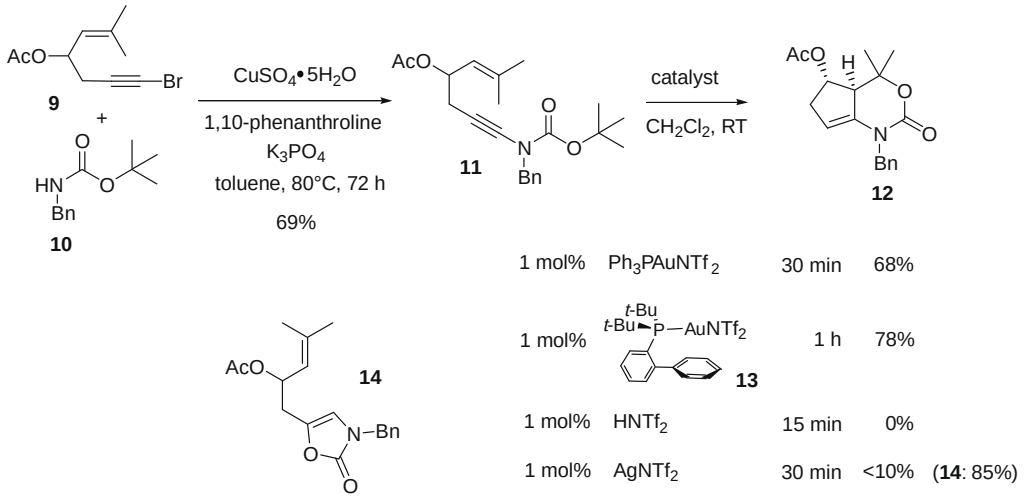
Enyne **11** was first chosen as a model substrate to validate our approach. It was synthesized in two steps following the procedure we previously reported (Scheme 4) [8]. Treatment of bromoalkyne **9** and *tert*-butyloxycarbamate **10** (1.2 equiv.) with $CuSO_4 \cdot 5H_2O$ (20 mol%), 1,10-phenanthroline (40 mol%) and K_3PO_4 (1.2 equiv.) in toluene at 80 °C for 72 h led to the formation of the desired *N*-alkynyl *tert*-butyloxycarbamates (**11**), which was isolated in 69% yield [13].

We were pleased to see that treating substrate **11** with 1 mol% of the crystalline and air stable $Ph_3PAuNTf_2$ gold complex [14] in dichloromethane at room temperature furnished the desired bicyclic compound **12** in 68% yield. The yield was improved to 78% when the biphenylphosphine based gold complex **13** [14] was used as the catalyst, even if the reaction time was longer in this case.

This new transformation, which can be described as a formal [4+2] cycloaddition of an *N*-alkynyl *tert*-butyloxycarbamate with an alkene [15], is remarkable from a synthetic point of view since two cycles and one new stereocentre are created from a linear substrate under mild reaction conditions. It is also noteworthy that the



Scheme 3. *External* nucleophilic addition versus *internal* nucleophilic addition.



Scheme 4. Formation and cyclization of enyne **11**.