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

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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.

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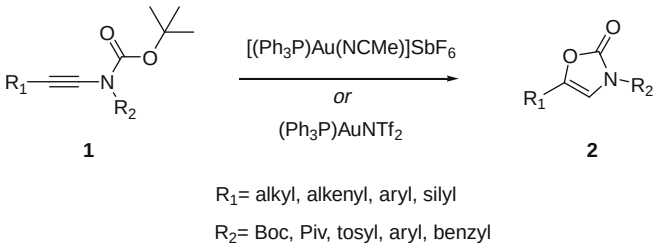
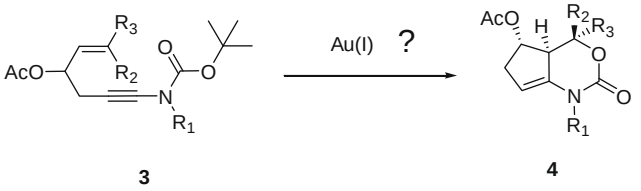


Scheme 1. Cyclization of *N*-alkynyl *tert*-butyloxycarbamates.



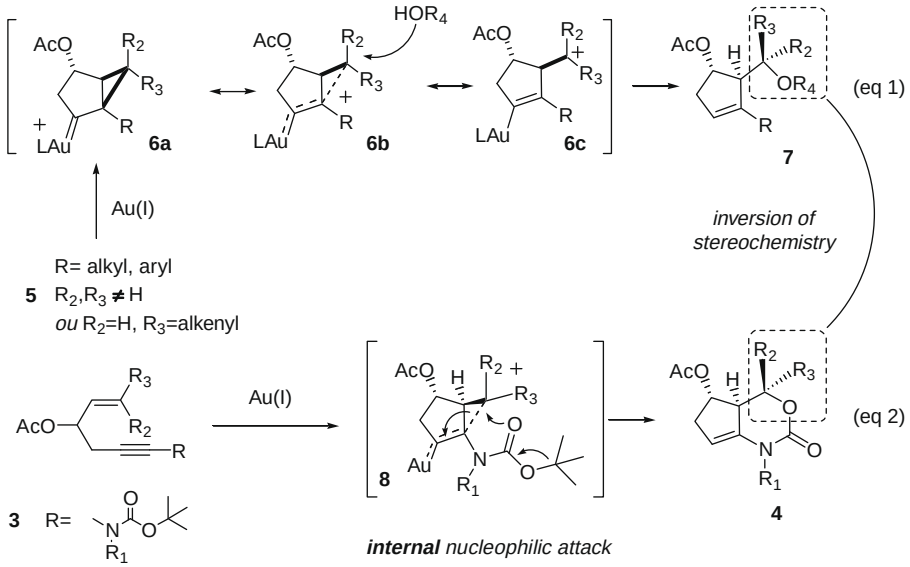
Scheme 2. Proposal of *N*-hex-5-enynyl *tert*-butyloxycarbamates cyclization.

2. Results and discussion

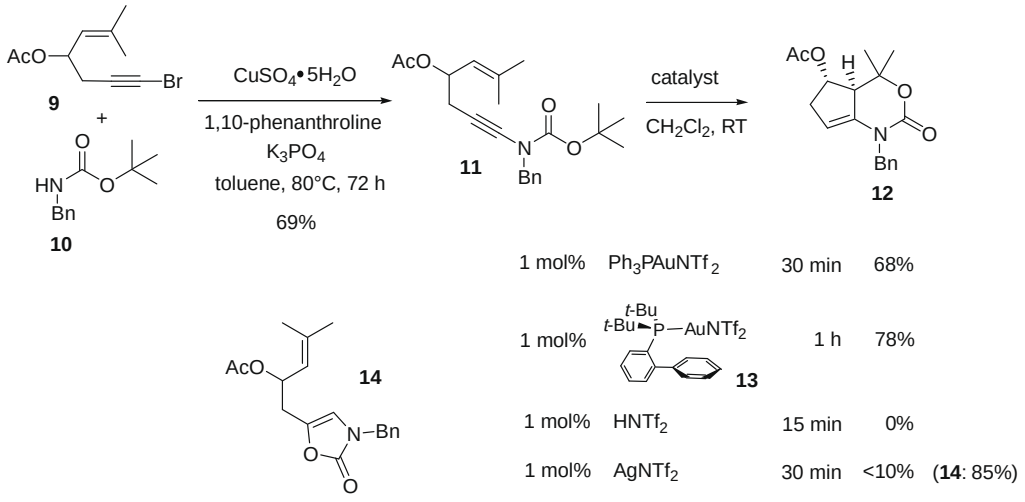
Enyne **11** was first chosen as a model substrate to validate our approach. It was synthesized in two steps following the procedure we previously reported (Scheme 4) [8]. Treatment of bromoalkyne **9** and *tert*-butyloxycarbamate **10** (1.2 equiv.) with $CuSO_4 \cdot 5H_2O$ (20 mol%), 1,10-phenanthroline (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.

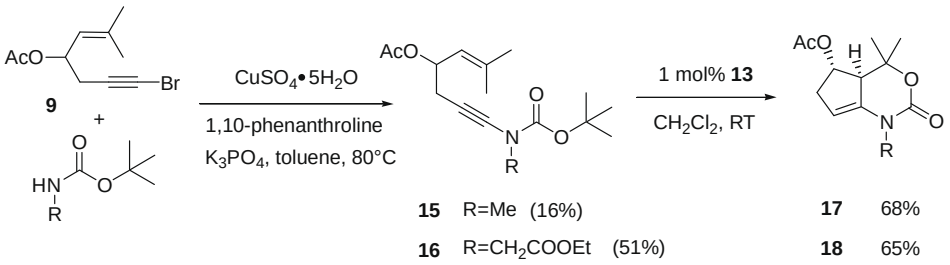
This new transformation, which can be described as a formal [4+2] cycloaddition of an *N*-alkynyl *tert*-butyloxycarbamate with an alkene [15], is remarkable from a synthetic point of view since two cycles and one new stereocentre are created from a linear substrate under mild reaction conditions. It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



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



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



Scheme 5. Formation and cyclization of enynes **15** and **16**.

previously reported 5-*endo* cyclization of the *tert*-butyloxycarbamate on the alkyne (Scheme 1) [7,8] did not significantly compete with this new transformation. The nucleophilic addition of the alkene moiety on the activated gold-alkyne complex seems to be a more favored process and only traces of oxazolones **14** could be observed when a gold complex was used as the catalyst. A control experiment led to the conclusion that $HNTf_2$ was not a suitable catalyst for this transformation. The reaction only furnished degradation products in this case. In contrast, the use of $AgNTf_2$ led to the rapid and clean conversion of enyne **11**. However, the desired bicyclic compound **12** was formed in a very low yield (<10%) and oxazolone **14** was surprisingly the major compound (85%) produced during the reaction.

The transformation was compatible with substrates bearing other groups on the nitrogen atom (Scheme 5).

The copper-catalyzed formations of enynes **15** and **16**, possessing either a methyl group or an ester group, were less efficient. However, they reacted comparably during the gold-catalyzed

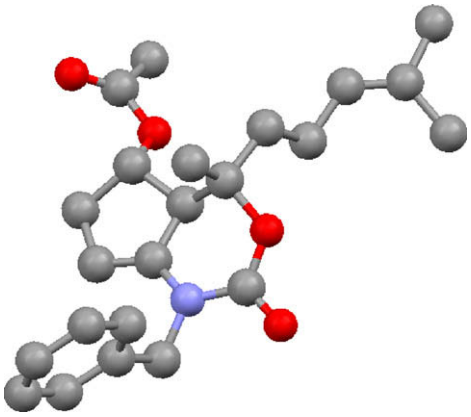


Fig. 2. Molecular structure of **20a**. Hydrogen atoms are omitted for clarity.

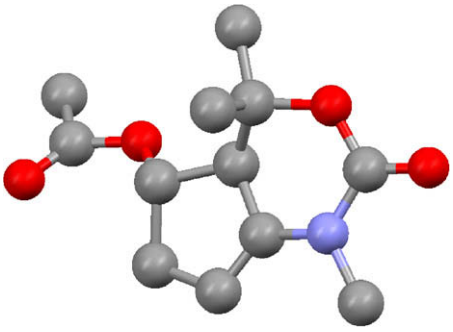


Fig. 1. Molecular structure of **17**. Hydrogen atoms are omitted for clarity.

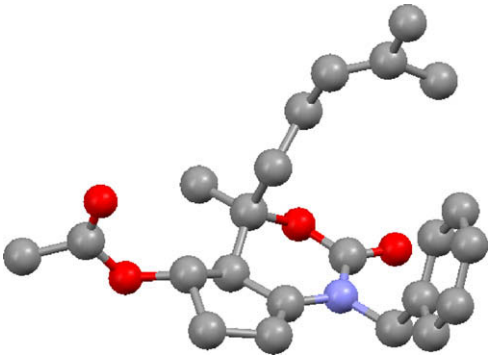
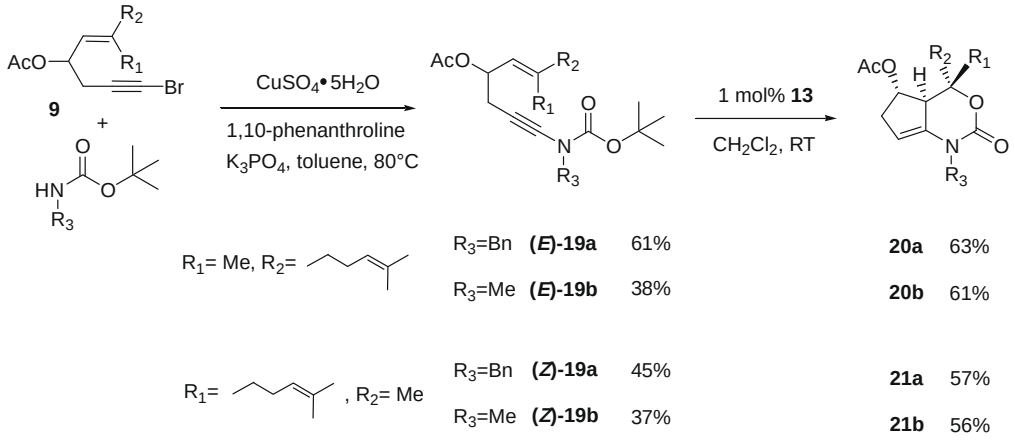


Fig. 3. Molecular structure of **21a**. Hydrogen atoms are omitted for clarity.



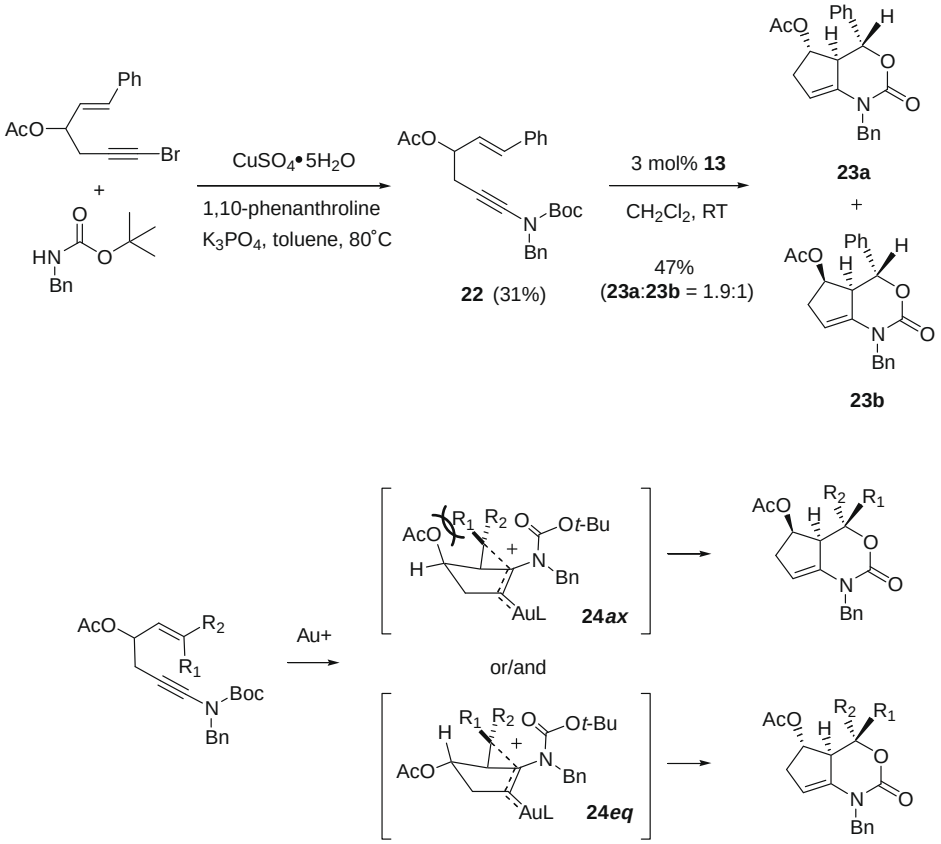
Scheme 6. Formation and cyclization of enynes (*Z*)-**19a–b** and (*E*)-**19a–b**.

cyclisation to produce bicyclic compounds **17** and **18** in respectively 68% and 65% yield. As noted in our previous study, the reactions were highly stereoselective, leading to the formation of single isomers [10]. The *cis* relationship between the acetoxy group and the hydrogen at the ring junction was determined by NMR analysis and confirmed by X-ray crystallography of compound **17** (Fig. 1).

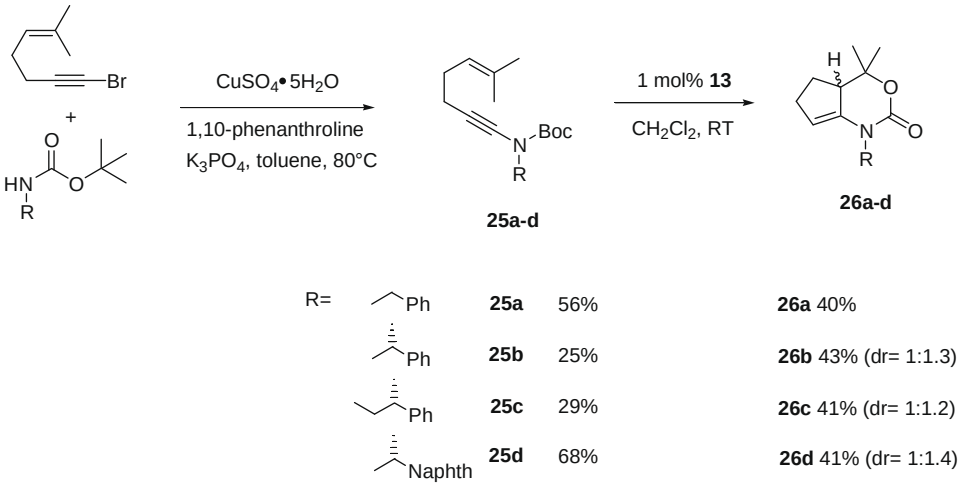
The reaction could also be applied to substrates possessing diversely substituted alkenes. A complete transfer of the chiral information from the *cis* or *trans* alkene to the final product was observed in the case of enynes **(*Z*)-19a–b** and **(*E*)-19a–b** with the stereoselective formation of two new contiguous stereocenters (Scheme 6). Bicycles **20a–b** and **21a–b** were thus obtained as single isomers in yields ranging from 56% to 63%.

The relative configuration of the new stereocentres were determined by NMR analysis and confirmed by X-ray crystallography of compound **20a** and **21a** (Figs. 2 and 3).

The [4+2] cycloaddition could also be performed with a disubstituted alkene possessing cation-stabilizing substituents on the alkene moiety, as attested by the reaction of substrate **22** derived from cinnamaldehyde (Scheme 7). The transformation was however less stereoselective and a diastereoisomeric mixture of compounds **23a** and **23b** was obtained. In the case of a trisubstituted



Scheme 7. Formation and cyclization of enyne **22**.



Scheme 8. Formation and cyclization of enynes **26a–d**.

alkene (R_1, $R_2 \neq H$), the reaction was stereospecific due to a strong steric interaction between the acetoxy group and R_1 which disfavored the formation of an intermediate such as **24ax**. The lack of a similar interaction for substrate **22** ($R_1 = H$) makes the transformation less selective since it allows the competitive formation of two intermediates of types ***24ax*** and ***24eq***.

We finally attempted to develop an asymmetric version of this [4+2] cycloaddition. We hoped that the presence of a chiral fragment on the nitrogen atom of substrates **25b–d** might induce some stereoselectivity in the reaction (Scheme 8). The reaction of substrate **25a**, bearing a simple benzyl group on the nitrogen atom, furnished the corresponding cyclized product **26a** in a moderate 40% yield. The yields were not improved when optically pure substrates **25b–d** were used (41–43%). Moreover, the results were highly disappointing since bicyclic compounds **26b–d** were obtained with a very poor selectivity.

3. Summary

In summary, we have shown that *N*-(hex-5-enynyl) *tert*-butyloxycarbamates could be cyclized into functionalized bicyclic carbamates under mild conditions by using a gold(I) complex as the catalyst. This transformation can be described as a formal [4+2] cycloaddition between an *N*-alkynyl *tert*-butyloxycarbamate and an alkene. Even if the yields are moderate (41–78%), the transformation is generally strereoselective and allows a rapid increase in structural complexity with the formation of two cycles and up to two new asymmetric centers. Further studies related to the conversion of the bicyclic carbamates thus obtained into more valuable compounds as well as studies concerning the development of other gold-catalyzed transformation of *N*-alkynyl carbamates are underway.

Supplementary material

CCDC 687781, 687782 and 687783 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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