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Synthesis of Functionalized Oxazolones by a Sequence of Cu(II)- and Au(I)-Catalyzed Transformations

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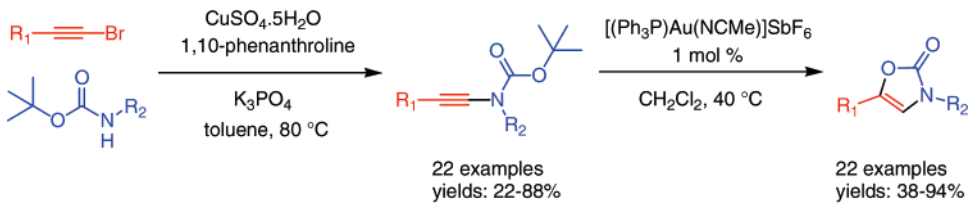
ABSTRACT



A study concerning a two-step sequence leading to the formation of diversely 1,5-disubstituted oxazolones is described. The mild conditions employed allow the efficient and rapid synthesis of a variety of such compounds via an initial Cu(II)-catalyzed coupling of a bromoalkyne with a secondary *tert*-butyloxycarbamate followed by a Au(I)-catalyzed cycloisomerization of the *N*-alkynyl *tert*-butyloxycarbamates thus obtained.

Oxazolones and their derivatives are attractive building blocks in organic synthesis. They have been sucessfully employed in a range of transformations mostly as an alkene unit in intramolecular Pauson−Khand reactions,[1] [4 + 2] cycloadditions,[2] palladium-catalyzed coupling reactions,[3] radical additions or cyclizations,[4] and in hydrogenation reactions for the synthesis of functionalized oxazolidinones.[5] The oxazolone motif is also found in a variety of synthetic substances exhibiting a wide range of pharmacological activities.[6] Surprisingly, there are only a few methods to synthesize polysubstituted oxazolones. Most use 1,2-aminoketone derivatives as starting materials and involve either high temperature,[7] strong basic[8] or acidic conditions,[9] or the use of toxic carbonylating reagents[10] which are not always compatible with the substitution pattern of the substrates.

Gold(I) complexes have emerged as efficient and mild catalysts[11] for the synthesis of various oxygen-containing

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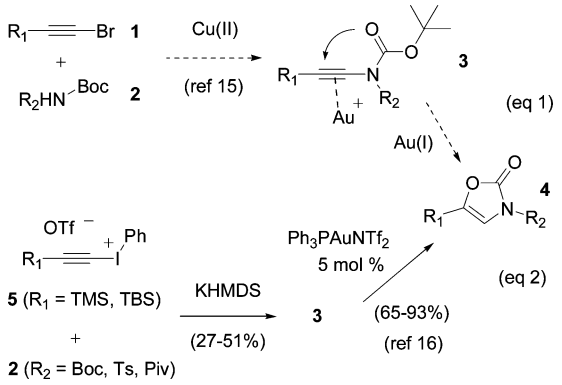
heterocycles[12] by intramolecular addition of an oxygenated nucleophile onto an alkyne or an allene. In this respect, special attention has been paid to the *tert*-butyloxycarbonyl moiety which was used as the nucleophilic partner in the gold-catalyzed formation of butenolides,[13a] dioxanones,[13b,c] dioxolanones,[13d,e] and oxazolidinones.[13f]

Following our ongoing efforts in developing new gold-catalyzed transformations,[14] we now report that diversely functionalized oxazolones could be efficiently synthesized by a gold(I) isomerization of *N*-alkynyl *tert*-butyloxycarbamates.

Scheme 1. Synthetic Approach to Functionalized Oxazolones



Our synthetic approach, depicted in Scheme 1 (eq 1), relies on a two-step sequence. The initial Cu(II)-catalyzed coupling of a bromoalkyne **1** with a *tert*-butyloxycarbamate **2**,[15] would lead to the formation of an *N*-alkynyl *tert*-butyloxycarbamate **3**. A subsequent 5-*endo* gold-catalyzed isomerization of **3** would furnish the desired oxazolone **4** (Scheme 1, eq 1). Indeed, while this work was in progress, Hashmi and co-workers validated this approach and reported that **3** could actually be isomerized into oxazoles **4**, using 5 mol % of $Ph_3PAuNTf_2$ (Scheme 1, eq 2).[16] Even if this procedure proved to be efficient (65−93% yield) and led to the desired products under mild conditions (0 °C or rt), we believed that our sequence could present a major advantage. Given the restricted access to functionalized iodonium salt **5** and its inefficient coupling with **3** (27−51%), it appeared to us that the Cu(II)-catalyzed coupling of **1** with **2** might advantageously broaden the scope of the transformation.[17]

We first investigated the Cu(II)-catalyzed step leading to the formation of the *N*-alkynyl *tert*-butyloxycarbamate **3**. Although numerous examples of direct copper-catalyzed cross-coupling of an alkynyl bromide with a carbamate, a sulfonamide, or an amide are described in the literature,[15] only one example of such a reaction was previously reported using a *tert*-butyloxycarbamate such as **2** as the reactant, and the yield was very low (12%).[15a]

In spite of the poor yield, attributed by the authors to steric hindrance,[15a] we decided to study this cross-coupling between a series of functionalized bromoalkynes **1a**−**g** and *tert*-butyloxycarbamates **2a**−**i** (Figure 1).

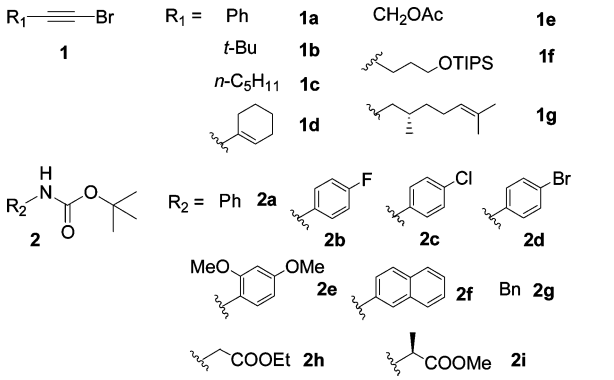


Figure 1. Bromoalkynes and *tert*-butyloxycarbamates used in the Cu(II)-catalyzed cross-coupling reaction.

Using slightly modified reaction conditions[15a] (20 mol % of $CuSO_4 \cdot 5H_2O$ and 40 mol % of 1,10-phenanthroline as the ligand with K_3PO_4 as the base in toluene at 80 °C), we were delighted to see that the cross-coupling was generally much more efficient than previously reported (Table 1). A wide range of *N*-alkynyl *tert*-butyloxycarbamates **3a**−**v** containing various functionalities were thus synthesized in yields ranging

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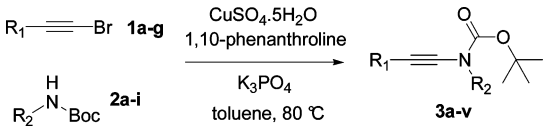
(17) The reaction reported by Hashmi and coworkers (ref 16) was limited to the use of substrates **3** bearing a hydrogen or a silyl group on the akyne and another electron-withdrawing group (Boc, Ts, Piv) on the nitrogen atom.

Table 1. Cu(II)-Catalyzed Formation of *N*-Alkynyl *tert*-Butyloxycarbamates[a]



entry	1	2	time (h)	product	yield (%)[b]
1	**1a**	**2a**	40	**3a**	80
2	**1a**	**2b**	16	**3b**	65
3	**1a**	**2c**	18	**3c**	68
4	**1a**	**2d**	16	**3d**	48
5	**1a**	**2e**	48	**3e**	22
6	**1a**	**2g**	48	**3f**	62
7	**1a**	**2h**	36	**3g**	70
8	**1a**	**2i**	48	**3h**	23
9	**1b**	**2a**	38	**3i**	24
10	**1c**	**2a**	52	**3j**	75
11	**1c**	**2g**	48	**3k**	69
12	**1d**	**2a**	67	**3l**	72
13	**1d**	**2c**	67	**3m**	80
14	**1d**	**2h**	67	**3n**	50
15	**1e**	**2a**	65	**3o**	55
16	**1e**	**2f**	48	**3p**	49
17	**1e**	**2g**	72	**3q**	49
18	**1e**	**2h**	62	**3r**	48
19	**1f**	**2a**	45	**3s**	88
20	**1f**	**2g**	62	**3t**	72
21	**1g**	**2a**	48	**3u**	74
22	**1g**	**2f**	48	**3v**	65

[a] Reaction conditions: **1** (1 equiv), **2** (1.2 equiv), $CuSO_4{\cdot}5H_2O$ (0.2 equiv), 1,10-phenanthroline (0.4 equiv), K_3PO_4 (2.4 equiv) in toluene (0.33 M based on **1**) at 80 °C. [b] Isolated yield.

from 22% to 88%.[18] To the best of our knowledge, this procedure represents the first general entry into synthesizing such compounds.

Having in hands an efficient procedure for the formation of **3**, we next focused our attention on the second step of the sequence, using carbamate **3j** as a model substrate (Table 2). While $Ph_3PAuNTf_2$[19] proved to be efficient in the procedure reported by Hashmi and co-workers,[16] poor results were obtained in our case with 1 mol % of this catalyst (entry 1).

The use of the more electrophilic $(pCF_3Ph)_3PAuNTf_2$[19] improved the conversion, but the yield of the desired oxazolone **4j** remained modest (40−52%, entries 2−3). Finally, the cationic $[Ph_3P\text{-}Au\text{-}(NCCH_3)]^+SbF_6^-$[20] complex, developed by Echavarren and co-workers, proved to be the catalyst of choice (entries 4−5). Under optimal conditions (1 mol % of $[Ph_3P\text{-}Au\text{-}(NCCH_3)]^+SbF_6^-$ in dichloromethane at 40 °C), oxazolone **4j** could be isolated in 74% yield. In the light of these preliminary results, experimental conditions as mentioned in entry 5 were retained for the study of the scope of this transformation.[21]

(18) The poor yields obtained in the case of **3e** and **3h** may be attributed to a greater steric hindrance around the nitrogen center.

(19) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133−4136.

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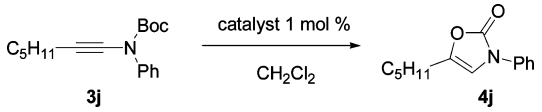
Table 2. Optimization of the Catalytic System[a]

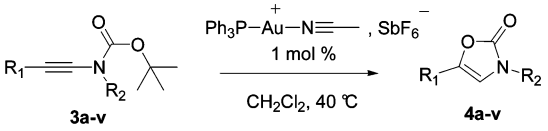


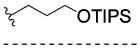
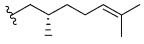
entry	catalyst	temp. (°C)	time	convrsn. (%)[b]	yield (%)
1	PPh_3AuNTf_2	20	7 h	63	28[c]
2	$(pCF_3Ph)_3PAuNTf_2$	20	72 h	85	52[d]
3	$(pCF_3Ph)_3PAuNTf_2$	40	2.5 h	100	40[d]
4	$[Ph_3P\text{-}Au\text{-}(NCCH_3)]^+SbF_6^-$	20	4.5 h	100	69[d]
5	$[Ph_3P\text{-}Au\text{-}(NCCH_3)]^+SbF_6^-$	40	30 min	100	74[c]

[a] Reaction conditions: 0.5 M substrate in CH_2Cl_2. [b] Estimated by ^1H NMR. [c] Isolated yield. [d] Estimated by ^1H NMR on the crude reaction mixture.

The reaction proved to be quite general, and various *N*-alkynyl *tert*-butyloxycarbamate **3a**−**v** reacted using 1 mol % of $[Ph_3P\text{-}Au\text{-}(NCCH_3)]^+SbF_6^-$ as the catalyst to furnish the corresponding oxazolones **4a**−**v** in generally good yields (38−94%) (Table 3). The time required to reach completion

Table 3. Au(I)-Catalyzed Formation of Oxazolones[a]

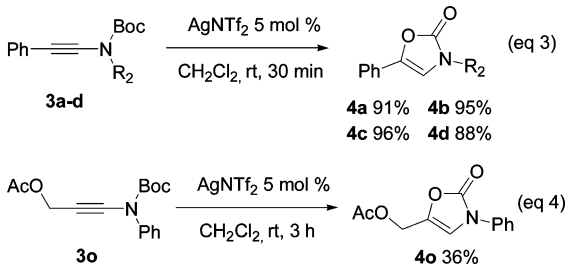


entry	substrate	R_1	R_2	time	product	yield [b]
1	**3a**	Ph	Ph	25 min	**4a**	83%
2	**3b**		*p*-FPh	10 min	**4b**	88%
3	**3c**		*p*-ClPh	10 min	**4c**	88%
4	**3d**		*p*-BrPh	10 min	**3d**	83%
5	**3e**		2,4(OMe)$_2$Ph	16 h	**4e**	85%
6	**3f**		Bn	16 h	**4f**	78%
7	**3g**		CH_2CO_2Et	12 h	**4g**	93%
8	**3h**			8 h	**4h**	94%
9	**3i**	*t*-Bu	Ph	2 h	**4i**	58%
10	**3j**	*n*-C_5H_{11}	Ph	30 min	**4j**	74%
11	**3k**		Bn	40 min	**4k**	50%[c]
12	**3l**		Ph	30 min	**4l**	78%
13	**3m**		*p*-ClPh	10 min	**4m**	94%
14	**3n**		CH_2CO_2Et	5 h	**4n**	70%
15	**3o**		Ph	40 min	**4o**	71%
16	**3p**		2-Napht	45 min	**4p**	88%
17	**3q**		Bn	20 min	**4q**	50%[c]
18	**3r**		CH_2CO_2Et	20 min	**4r**	49%
19	**3s**		Ph	1 h	**4s**	69%
20	**3t**		Bn	40 min	**4t**	38%[c]
21	**3u**		Ph	30 min	**4u**	71%
22	**3v**		2-Napht	3 h	**4v**	80%

[a] Reaction conditions: **3** (1 equiv), $[(Ph_3P)Au(NCMe)]SbF_6$ (0.01 equiv) in refluxing CH_2Cl_2 (0.5 M). [b] Isolated yield. [c] Yield determined by ^1H NMR on the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

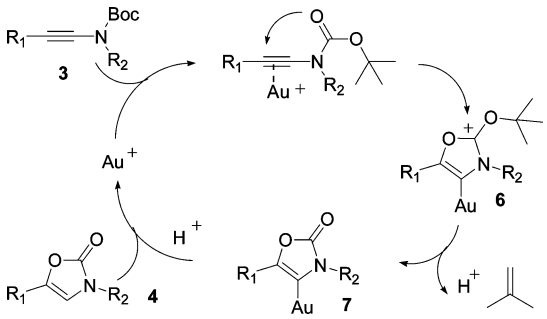
was in most cases shorter than 2 h. Various substituted aryl, benzyl, or acetyl groups were tolerated on the nitrogen atom. The experimental conditions were also compatible with a variety of commonly used functionnal groups such as a propargylic acetate (**3o**−**r**), a silyl ether (**3s**,**t**), or an alkene (**3l**−**n** and **3u**,**v**). Substrates possessing a benzyl group on the nitrogen atom (**3k**, **3q**, and **3t**) furnished the desired products in moderate yields (38−50%),[22] but surprisingly, these proved to be instable and could not be isolated.

In the cases where the formation of the oxazolone was rapid enough (substrates **3a**−**d**), we attempted to run the reaction using 5 mol % of $AgNTf_2$ as the catalyst (eq 3). We were delighted to see that the corresponding oxazolones **4a**−**d** could be obtained in excellent yields (88−96%). These conditions were, however, not general. Substrate **3o** led, for instance, to a poor 36% yield of oxazolone **4o** (eq 4).



To account for these observations, a mechanism for the formation of the oxazolones is proposed in Scheme 2. Gold(I) activation of the triple bond in *N*-alkynyl *tert*-butyloxycarbamate **3** promotes the formation of the stabilized cationic species **6**. Fragmentation of the C−O bond of the *tert*-butyloxy group in **6** then leads to the formation of the neutral vinyl−gold species **7,** which is subsequently protonated to finally furnish oxazolone **4**.

Scheme 2. Proposed Mechanism



In summary, we have developed an efficient two-step sequence for the synthesis of oxazolones from readily available bromoalkynes and *tert*-butyloxycarbamates. The Cu(II)-catalyzed cross-coupling reaction proved to be a general and efficient method for the preparation of various *N*-alkynyl *tert*-butyloxycarbamates. These were converted under mild conditions into a range of diversely substituted oxazolones by using a low loading of a gold(I) catalyst. Further studies related to the gold-catalyzed isomerization of other *N*-alkynyl carbamates are underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Brønsted acid ($HNTf_2$) did not promote the reaction and led to extensive decomposition of the substrate. Silver salts ($AgNTf_2$, $AgSbF_6$) did promote the reaction (53%, 64%) but their efficiency proved limited to a few substrates (see eqs 1 and 2).

(22) The yield was determined by ^1H NMR on the crude reaction mixture.