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Gold Catalysis: Mild Conditions for the Synthesis of Oxazoles from *N*-Propargylcarboxamides and Mechanistic Aspects

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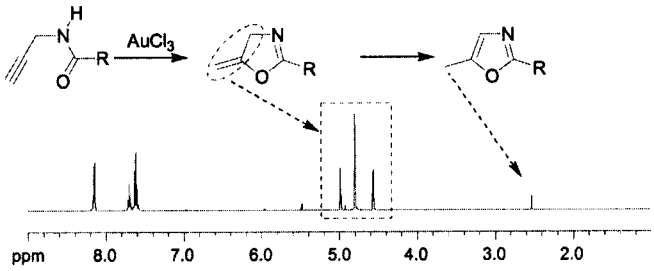
ABSTRACT



2,5-Disubstituted oxazoles are synthesized from the corresponding propargylcarboxamides under mild reaction conditions via homogeneous catalysis by $AuCl_3$. While monitoring the conversion via ^1H NMR spectroscopy, an intermediate 5-methylene-4,5-dihydrooxazole can be observed and accumulated up to 95%, being the first direct and catalytic preparative access to such alkylidene oxazolines. The intermediate was fully characterized and can be trapped at −25 °C for several weeks. Deuteration experiments show a stereospecific mode of the two first steps of the reaction.

The substituted oxazole fragment is a structural motif that occurs in a huge number of natural products. In particular, substances of marine origin show a variety of oxazole patterns, some containing up to four oxazole rings.[1] Most of these compounds show significant biological activities as antitumor agents, antileukemia agents, antiviral agents, antifungal agents, ichthyiotoxic agents, herpes simplex virus type 1 (HSV-1) inhibitors, serine-threonine phosphatase inhibitors, antibacterials, antialgicidals, and peripheral analgesics.[1]

Methods for the direct synthesis of the oxazole ring range over a variety of reactions and starting materials.[1] These cover, e.g., rearrangements, oxidations of the corresponding oxazolines, metal-mediated additions of diazoalkanes to nitriles, and a number of cyclizations with condensation of water, most of these having harsh conditions.

A few years ago, Hacksell et al.[2] showed that propargylic amides may be cyclized to the corresponding oxazoles under basic reaction conditions, so far the most popular method.[3] The proposed reaction mechanism of this 5-*exo*-*dig* cycliza-

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(2) (a) Nilsson, B. M.; Hacksell, U. *J. Heterocycl. Chem.* **1989**, *26*, 269. (b) Nilsson, B. M.; Vargas, H. M.; Ringdahl, B.; Hacksell, U. *J. Med. Chem.* **1992**, *35*, 285.

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tion proceeds via an allenic intermediate that could be monitored during the reaction via ^{1}H NMR spectroscopy.[2a] Until then, that cyclization was accomplished only by using reagents such as H_2SO_4 or $Hg(OAc)_2$ at higher temperatures.[4] With mercury(II) also a different mode of reaction, the formation of a ketone, has been observed.[5] Recently, Cacchi et al. used catalytic amounts of Pd(0) complexes to perform a related coupling−cyclization in the presence of aryl iodides.[6] There, an initial alkyne−arene coupling followed by a base-catalyzed (NaO^{t}Bu) isomerization seemed to be operative. Costa et al. reported the Pd(II)-catalyzed oxidative carbonylation of disubstituted prop-2-ynylcarboxamides to deliver 5-alkoxycarbonylmethylene-3-oxazolines.[7]

The reactions with both Hg(II) and Pd(II) are probably initiated by an activation of the triple bond by the electrophilic metal species. Because gold has recently proven to be superior to these species,[8] we now investigated the reaction of Au(III) with a range of amides **1**.

As shown in Table 1, the concept works nicely; the reaction can either be run in dichloromethane at ambient temperature or acetonitrile at 45 °C with 5 mol % of catalyst loading to yield the products in good to excellent yields. It is noteworthy that a number of functional groups are tolerated under these conditions; however, the terminal alkyne is crucial for the reaction, which can be seen with amide **5** that shows no conversion at all (Figure 4). The conversion of starting material is apparently affected by intramolecular coordinating functionalities and electronic factors as reflected by the reaction times for furans **1c**, **1e** or esters as in **1h**. However, moving these away from the reaction center, the reaction becomes more and more feasible (entry **i** and **j**).

A characteristic of the very mild and neutral reaction conditions is the direct observation of the intermediate methylene-3-oxazoline **3** (Figure 1), a species never observed in metal catalysis before with substrates that do not possess a disubstitution that blocks an isomerization to the aromatic heterocycle. In general, this class of compounds is only known from three publications,[9] two of them covering heteroatom-substituted derivatives.[9b,c] The exocyclic olefin **3** could be observed during the reaction via ^{1}H NMR (Figure 1a).[9a] Signal assignment of H^a, H^b and $H^{c1/2}$ would be possible by the NOE of 6% in a NOE difference spectrum but is problematic due to the scalar allylic coupling. Similar NOE data has quite recently been published by Toste et al. for the product of a gold-catalyzed Conia-ene reaction.[9d] As final proof, we measured the proton-coupled ^{13}C spectrum of **3** (Figure 2a). The endocyclic methylene carbon shows a tdd with $^1J_{CH}$ = 145.6 Hz and $^3J_{CH}$ = 2.5 Hz (*cis*), 7.9 Hz (*trans*). The

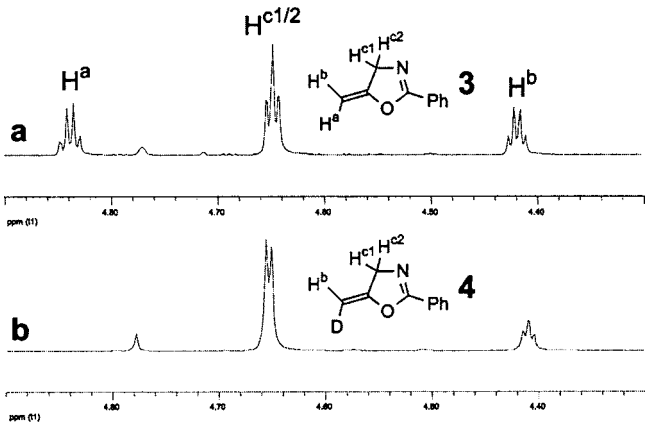
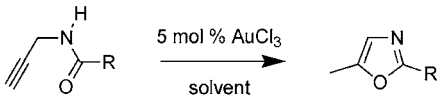
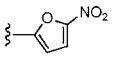
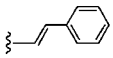


Figure 1. ^{1}H NMR (a) during the reaction of **1b** showing intermediate **3** and (b) during reaction of **7**.

Table 1. $AuCl_3$-Catalyzed Cycloisomerization of Propargylic Amides



1 2

run	1	R	solvent	T/°C	t/hrs	yield [a]
1	**a**	Me	MeCN	45	15	>95 [b]
			DCM	20	12	>95
2	**b**	Ph	MeCN	20	15	>95 [b]
			DCM	20	12	>95
3	**c**		MeCN	45	96	88 [b]
			DCM	20	48	>95
4	**d**		MeCN	20	96	>95 (50)
			DCM	20	48	>95 (88)
5	**e**		DCM	20	48	0
6	**f**		MeCN	45	3	>95
			DCM	20	12	>95 (98)
7	**g**		MeCN	20	96	>95 (91)
			DCM	20	12	>95 (73)
8	**h**		MeCN	20	15	0
9	**i**		MeCN	50	2	48 (40)
10	**j**		MeCN	50	2	91 (86)
11	**k**		MeCN	50	18	58 (50)

[a] In %, by NMR, isolated yield in parentheses. [b] Compound known.

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corresponding methylene carbon of **4** only shows a td, leaving $^3J_{CH} = 2.5$ Hz (*cis*) as the only remaining long-range C−H coupling. The $^3J_{CD} \approx 1.2$ Hz (*trans*) is not resolved (Figure 2b).

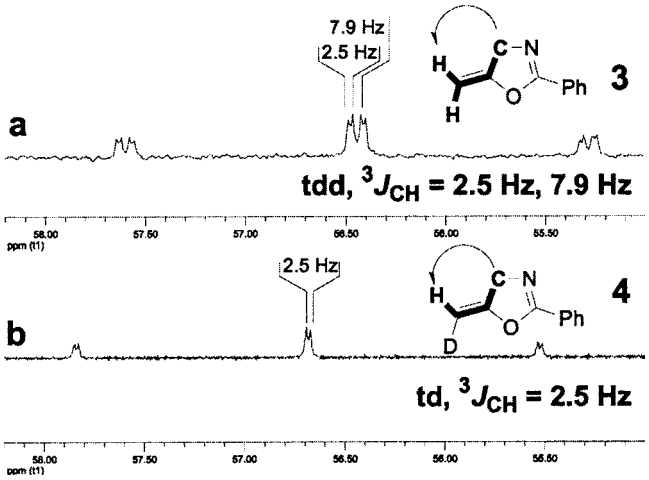


Figure 2. Proton coupled ^{13}C NMR of (a) **3** and (b) **4**.

In addition, quantum mechanical calculations (B3LYP/6-31G** including ZPE corr.) show that olefin **3** is thermodynamically −25.7 kcal/mol more stable than amide **1b**. Aromatization to oxazole **2b** sets free an additional −16.8 kcal/mol. For amide **1a** to the corresponding intermediate and oxazole **2a** only −21.4 and −15.5 kcal/mol are obtained, respectively. Control experiments with our substrates and Pd(II) complexes in the absence of aryl iodides afforded no conversion of the starting material.

This now allows a deeper mechanistic insight. Both the formation of **3** and its conversion to an oxazole can be directly observed without the potentially disturbing influences of additional substituents on the substrate or ligands on the metal.

Figure 3 shows that intermediate **3** can be enriched to about 95%, when running the reaction with amide **1b** in dichloromethane at room temperature. At −25 °C, **3** can be stored and investigated for weeks. Higher stabilities under these conditions are only observed with substrates such as **6**, which cannot isomerize to the more stable oxazole by a prototopic isomerization.[10]

Using the deuterated amide **7**, we furthermore observe only one single diastereomer **4** during the conversion showing that the activation of the alkyne and the subsequent addition of the oxygen nucleophile is strictly stereospecific (Figure 1b)! This suggests that the carbonyl-oxygen stereoselectively attacks the π-coordinated alkyne from the backside and the intermediate aurated enolether species is then stereospecifically proto-demetalated to **3** (Scheme 1).

This is in contrast to the work of Teles et al., who calculated a *syn* mode for the gold(I)-catalyzed addition of alcohols as oxygen nucleophiles to alkynes.[11] Maybe an H···Au^I interaction accounts for the different stereochemical pathway with a front-side attack.

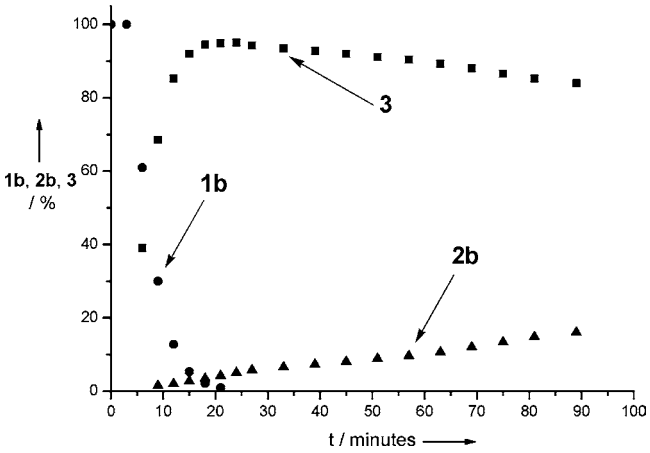


Figure 3. Time/concentration profiles of amide **1b**, intermediate **3**, and oxazole **2b** as monitored via ^{1}H NMR.

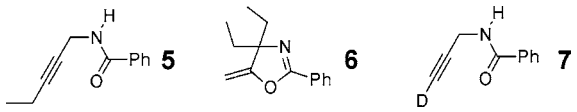
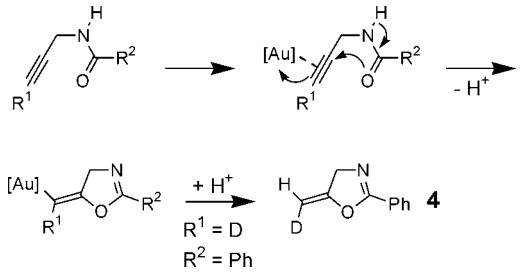


Figure 4. Substrates for mechanistic investigations.

Scheme 1. Proposed Reaction Mechanism



In addition, the formation of **4** excludes a pathway of an initial isomerization[12] to the allenic imidate (as known for propargylic acetates with Ag(I)) and subsequent nucleophilic attack at the central carbon of the allene.

In conclusion, gold(III) again proved its high efficiency for the electrophilic activation of C−C multiple bonds. The mild reaction conditions allow mechanistic insight; both the oxyauration and the proto-demetalation steps are highly diastereoselective, and 4,4-unsubstituted methylene oxazolines are now easily observed. Because these new and interesting compounds can be accumulated up to 95%, it will be

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interesting to test whether they can react with electrophiles other than a proton, then leading to different functionalized products.

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Supporting Information Available: Reaction and catalysis conditions, as well as characterization of products and crystal structures of **1c,d,f,h,j,k and 2g,k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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