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Cyclization of Propargylic Amides: Mild Access to Oxazole Derivatives

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In memorial of Dr. Jan P. Weyrauch

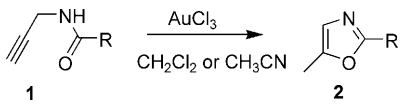
Abstract: The substrate scope, the mechanistic aspects of the gold-catalyzed oxazole synthesis, and substrates with different aliphatic, aromatic, and functional groups in the side chain were investigated. Even molecules with several propargyl amide groups could easily be converted, delivering di- and trioxazoles with interesting optical properties. Furthermore, the scope of the gold(I)-catalyzed alkylidene synthesis was investigated. Further functionalizations of these isolable intermediates of the oxazole synthesis were developed and chelate ligands can be obtained. The use of Barluenga's reagent offers a new and mild access to the synthetically valuable iodoalkylideneoxazoles from propargylic amides, this reagent being superior to other sources of halogens.

Keywords: cyclization · fluorescence · gold catalysis · methyleneoxazolines · oxazoles · propargylic amides

Introduction

The utilization of gold catalysts in the field of organic chemistry is one of the hot topics in current research.[1] Most of these reactions are atom economical and in comparison to other transition-metal catalysts the reaction conditions are remarkably mild in most cases. Among these transformations, the intramolecular addition of heteroatom nucleophiles to carbon–carbon triple bonds plays an important role as powerful tool for the synthesis of various heterocycles. The first evidence for this reaction pattern was contributed by Utimoto et al. in 1987 who investigated an intramolecular hydroamination of alkynes, which delivered tetrahydropyridines after a subsequent isomerization.[2] In 2000, our group published the gold-catalyzed transformation of furans by a 5-*endo-trig* cyclization of allenyl ketones, which provided evidence that even carbonyl oxygen atoms can serve as nucleophiles in gold-catalyzed rearrangements.[3] Based on these findings, a large family of gold-catalyzed heterocycle syntheses was developed by different groups.[4]

Inspired by Arcadi, Cacchi, and co-workers, who published a Pd^0-catalyzed coupling–cyclization sequence for the synthesis of disubstituted oxazoles,[5] in 2004 we contributed the gold-catalyzed synthesis of oxazoles **2** formed by a 5-*exo-dig* cyclization of *N*-propargyl carboxamides **1** (Scheme 1).[6] This transformation is of high importance, as the motif of disubstituted oxazoles can often be found in natural products and plenty of these compounds exhibit interesting pharmaceutical potential, for example, as antitumor agents, antifungal agents, herpes simplex virus type 1



1 2

Scheme 1. Gold-catalyzed oxazole synthesis (R = alkyl, vinyl, aryl).

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(HSV-1) inhibitors, serine–threonine phosphate inhibitors, and antibacterials.[7]

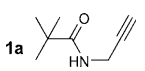
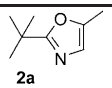
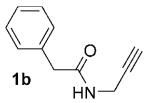
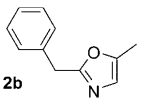
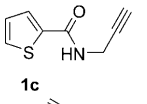
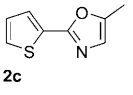
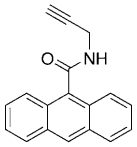
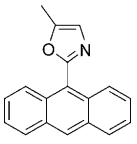
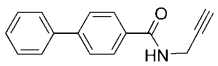
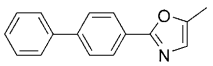
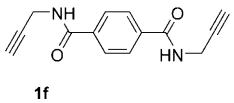
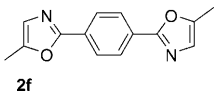
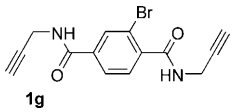
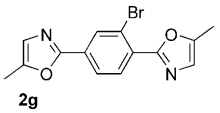
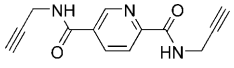
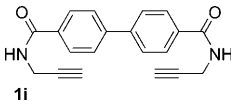
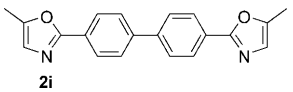
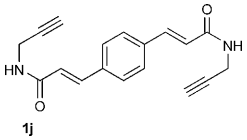
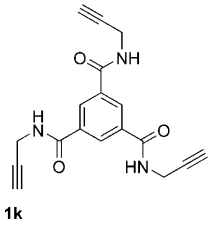
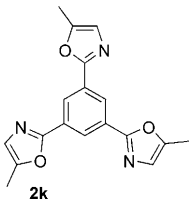
As most of the above-mentioned compounds are highly functionalized, the mild conditions[8] of the gold-catalyzed oxazole synthesis make it extremely attractive in comparison to the classical routes through condensation reactions, which often demand harsh reaction conditions.[7] Hence, this protocol has even attracted industrial chemists and patents containing the gold-catalyzed transformation as the key step can be found.[9]

In the meantime, there are several reports in the literature concerning the use of different ligand systems at the gold center,[10] the use of other transition metals as catalysts,[11] as well as a Brønsted acid-catalyzed variant (under reflux conditions).[12] Herein, we report our latest results in this important field, on both synthetic as well as further mechanistic aspects of this fascinating and useful reaction.

Results and Discussion

Our first goal was to extend our methodology to a broader array of starting materials including substrates bearing even several propargylic moieties for multiple reactions. Table 1 shows the results of these cyclizations. For the substrates containing only one propargylic amide side chain, all substrates underwent a smooth reaction to furnish *tert*-butyl- (**2a**), benzyl- (**2b**), thiophenyl-substituted oxazoles **2c** (Table 1, entries 1–3) as well as the bulky anthracenyl-substituted oxazole **2d** (Table 1, entry 4) and the biphenyl substrate **2e**, most of them in excellent yields. Concerning the interesting optical abilities of aryl-substituted oxazoles and their application as luminophores,[13] we investigated the reactions of substrates containing up to three propargylic moieties in one molecule. To our delight, most of these substrates showed full conversion to the corresponding oxazoles (Table 1, entries 6, 7, 9) for the bifunctionalized, and even substrate **1k** (Table 1, entry 11), which contains three propargylic moieties, delivered **2k** as a single product in a remarkable yield of 86%. The X-ray crystal structure analysis of compound **2f** (Figure 1) provides unambiguous proof for the formation of the two oxazole moieties.[14] All of the reactions with substrates containing more than one propargylic tether were carried out at slightly elevated temperature,

Table 1. Substrate scope of the gold-catalyzed oxazole synthesis with $AuCl_3$.

Entry	Starting material	Solvent	Time	Product	Yield of **2** [%]
1	 **1a**	CH_2Cl_2	21 h	 **2a**	100[a]
2	 **1b**	CH_2Cl_2	21 h	 **2b**	70
3	 **1c**	CH_2Cl_2	21 h	 **2c**	63
4	 **1d**	CH_2Cl_2	5 min	 **2d**	97
5	 **1e**	CH_2Cl_2	5 min	 **2e**	94
6	 **1f**	CH_2Cl_2	12 h	 **2f**	99
7	 **1g**	CH_3CN	5 h[b]	 **2g**	45
8	 **1h**	CH_3CN	72 h	no conversion	–
9	 **1i**	CH_2Cl_2	6 h[b]	 **2i**	60
10	 **1j**	CH_2Cl_2	12 h	no conversion[c]	–
11	 **1k**	CH_2Cl_2 or CH_3CN	12 h[b]	 **2k**	86

[a] NMR conversion; product too volatile to be isolated. [b] Reaction at 50 °C. [c] This is most probably caused by the insolubility of the starting material.

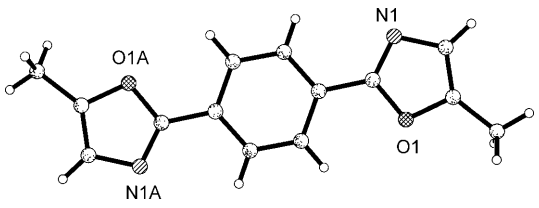


Figure 1. Plot of the structure of **2f** in the solid state.

which was essential because of the low solubility of the starting materials. In the case of substrate **1j** (Table 1, entry 10) this is most probably the reason for the lack of conversion; the compound was neither soluble in dichloromethane nor in CH_3CN even at boiling temperatures.

By decreasing the electron density of the central aromatic systems in **1g** and **1h** (Table 1, entries 7 and 8), it could be demonstrated that the limitations of this methodology are electron-poor substrates (in the case of electron-poor pyridine substrate **1h** no conversion at all took place).

Table 2 shows the luminescence abilities of some representative examples (see also Figure 1). The UV absorption of the compounds was in the 300–400 nm region, depending

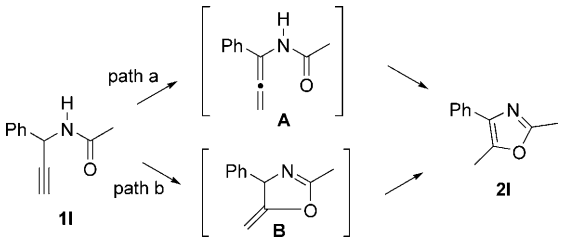
Table 2. Luminescence data of some representative aryloxazoles.

Entry	**2**	λ_{max} (Abs.) [nm]	ε_{max} [$L\,mol^{-1}\,cm^{-1}$]	log ε_{max}	λ_{max} (Em.) [nm]	$\Delta\tilde{\nu}$ [cm^{-1}]
1	**d**	376	6343	3.80	469	5274
2	**e**	302	32452	4.51	359	5257
3	**i**	324	47400	4.68	387	5024
4	**k**	290	53166	4.73	369	7382

on the grade of conjugation. While compound **2d** (Table 2, entry 1) showed a maximum absorption at 376 nm, compound **2i** had a maximum absorption at 324 nm due to a hypsochromic shift induced by the loss of conjugation between the two phenyl rings. The absorption at the lowest wavelength of **2k** (Table 2, entry 4) clearly indicates that the three attached oxazole rings are not coplanar to the central aromatic core. Even **2i** with three single bonds between the four aromatic moieties showed a higher maximum absorption at 324 nm.

The fluorescence spectra of **2d** showed a maximum emission at 469 nm that was visible as a green luminescence, whereas the other compounds showed blue luminescence with maximum emissions between 359–387 nm. The highest stokes shift of 7382 cm^{-1} was monitored for compound **2k**, initiated by the three oxazole moieties.

Mechanistic aspects: Contemporaneous to our initial publication on the gold-catalyzed oxazole synthesis, Uemura et al. contributed a highly innovative Ru/Au-catalyzed tandem sequence of propargylic alcohols and amides to the corresponding oxazoles.[15] Their mechanistic concept considered a ruthenium-catalyzed condensation (5 mol% of a diruthenium complex) of the starting material to form the intermediate propargyl amides **1**, which after isomerization to the allene intermediates **A** (Scheme 2, path a) finally give the oxazole products **2** with 10 mol% of $AuCl_3$ in a one-pot



Scheme 2. Possible mechanistic pathways for the oxazole formation.

reaction. They claimed the observation of intermediate **A** by in situ ^1H NMR spectroscopy. A similar reaction pattern was reported by Hacksell et al., who reported a base-catalyzed isomerization of propargylic amides through allenic intermediates.[16] But the ^1H NMR data reported by Uemura et al. did not match the symmetry of intermediate **A**, which should show only one resonance for the allenic CH_2 group, but two different resonances were reported in footnote 7 of the publication. Furthermore, such an intermediate would contradict our mechanistic findings:[6] As we considered the participation of intermediate dihydrooxazoles (Scheme 2, path b) in our publication, further experimental clarification of the mechanism was required. For a direct comparison, we synthesized the propargylic amide **1l**, which was also generated in situ during Uemura's one-pot version of this reaction and had been studied by in situ ^1H NMR spectroscopy by Uemura et al. The low-temperature DEPT NMR spectra of the reaction mixture (Figure 2) clearly reveal that only path b is operating for the gold-catalyzed cyclization, unambiguously proven by the tertiary carbon atom at $\delta =$ 70.7 ppm (the allenic intermediate does not contain any methine carbon atom).

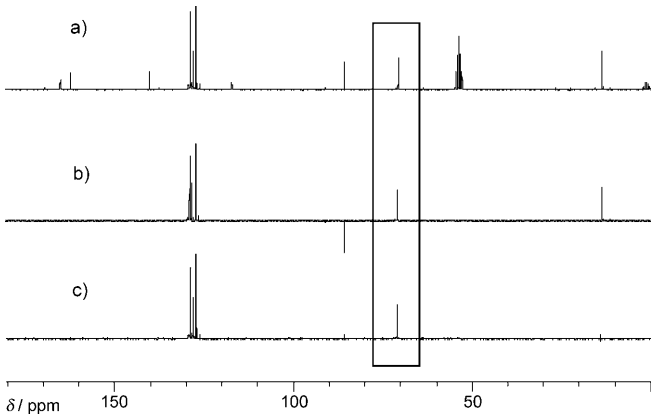
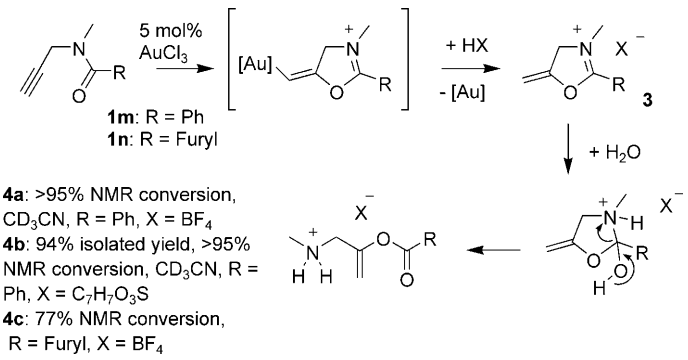


Figure 2. a) $^{13}C\{^1H\}$ NMR spectrum, b) DEPT 135 NMR spectrum, and c) DEPT 90 NMR spectrum. All spectra were taken during the conversion of **1l** with 5.0 mol% $AuCl_3$ at −20 °C.

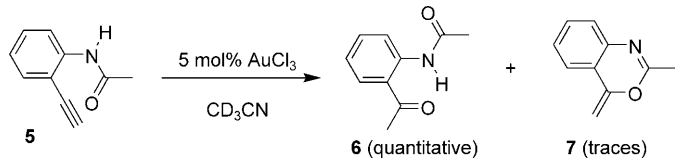
From a mechanistic point of view, it is obvious, that a proton is needed for the regeneration of the active catalyst. With this in mind, we prepared substrates **1m** and **1n** (Scheme 3) containing a methyl-substituted nitrogen, and



Scheme 3. Conversion of *N*-methyl propargylic amides.

added external proton sources such as *p*-TsOH or HBF_4. The $AuCl_3$-catalyzed conversion of these substrates did not form oxazoles, instead addition of water to the intermediate dihydrooxazonium salts **3** and a subsequent ring opening delivered vinylesters **4a–c** with allylamine substructures. Interestingly, no aromatization of the intermediates was monitored, indicating that the intermolecular water addition seems to be faster than the aromatization step.

The experiment aimed at generating a possible 6-*exo*-*dig* cyclization of the aniline-derived substrate **5** (Scheme 4) showed only traces of the desired product. In this case, the



Scheme 4. Intermolecular water addition versus intramolecular 6-*exo*-*dig* cyclization.

competing water addition leading to **6** turned out to be much faster.

Dihydrooxazoles: In our previous report on the gold-catalyzed cyclization of trichloroacetimidates to the corresponding oxazoles by hydroamination,[17] Au^I salts turned out to be very effective for the conversion to the alkylidene oxazoles, previously only known as reactive intermediates. Inspired by these results, we looked into one example for an Au^I-catalyzed conversion of propargylic amides as well. Under these conditions we were able to isolate the methylene dihydrooxazole as a stable compound even after purification on silica. To further explore the scope of this isomerization, we converted a series of different propargylic amides by using Au^I catalysts (Table 3). The scope of this reaction turned out to be very broad. Entries 1–5 in Table 3 present substrates which contain aliphatic moieties in the side chain. Apart from substrate **1q** (Table 3, entry 4), all of the substrates underwent smooth conversion. Here the presence of an additional alkynyl moiety led to a loss of selectivity of the reaction and only 8% of the fairly unstable product **8q** could be isolated. Even substrate **1r** (Table 3, entry 5) with the sterically demanding adamantyl substituent delivered remarkable yields. The high functional group tolerance of this reaction could be demonstrated with an array of different ester substrates (Table 3, entries 6–8). Interestingly, the directly attached ester moiety in substrate **1s** (Table 3, entry 6) led to aromatization, while the other ester substrates (Table 3, entries 7 and 8) delivered the methyleneoxazolines in high yields. Next we investigated aryl-containing substrates. To our delight all of the tested substrates delivered the corresponding methyleneoxazolines in good to excellent yields, independent of the electronic properties of the aromatic systems (Table 3, entries 9–13). Figure 3a shows the results of the X-ray crystal structure analysis of compound **8v**.[14] The fully conjugated system of the molecule leads to a planar alignment in the solid state. Substrates containing aromatic heterocycles as substituents showed a dependency on the electronic properties of the aromatic system. While thiophene substrate **1c** (Table 3, entry 14) and furan substrates **1z** and **1aa** (Table 3, entries 15 and 16) furnished good to excellent yields, only poor yields were accomplished with the electron-poor furan substrate **1ab** (Table 3, entry 17) as well as the pyridine derivative **1ac** (Table 3, entry 18). We then tested substrates that contained two propargylic moieties. The same tendencies mentioned above were visible for these compounds as well (Table 3, entries 19–23). The limits lay once again in electron-poor substrates like **1h** (Table 3, entry 23). Here the position of the heteroatom of the central pyridine led to a differentiation between the two alkynyl moieties. Only the electron-richer side chain reacted to form dihydrooxazole **8f**. Two of the products formed single crystals suitable for X-ray structure analysis. The illustrations of the X-ray structure data of **8ad** and **8f** in Figure 3b and c respectively, once more reveal the high chemoselectivity of these transformations.[14] The products **8ac** and **8ad** can only be formed with the Au^I catalysts, as these products are chelating ligands and poison the square planar Au^{III} complexes by product inhibition, but not the linear Au^I complexes.

Further functionalization: Our next aim was to further functionalize the methyleneoxazolines. Inspired by literature reports on the trapping of intermediate vinylgold compounds[18] with electrophilic reagents,[19] we reacted different propargylic amides in the presence of electrophilic *N*-halosuccinimides and the gold catalyst (Table 4). The results demonstrate that the expected halomethyleneoxazolines **10** were not formed in the reaction of the gold intermediate with the electrophile before the proto-demetalation step (Scheme 5). Instead, the formation of halogen-substituted halomethyloxazoles **9** occurred, unfortunately in low yields,

Table 3. Au^{I}-catalyzed formation of methylendihydrooxazoles.

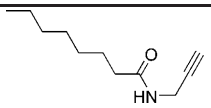
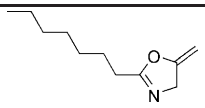
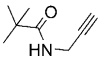
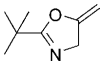
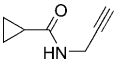
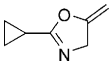
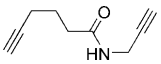
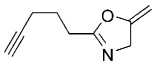
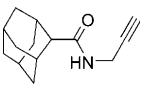
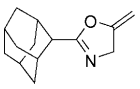
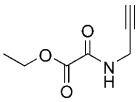
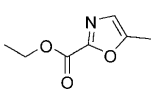
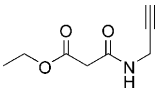
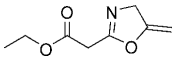
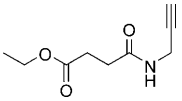
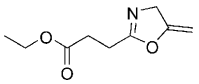
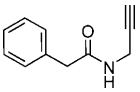
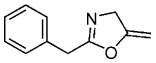
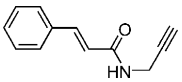
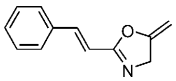
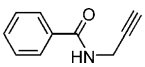
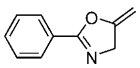
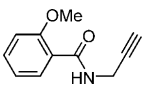
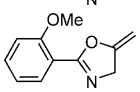
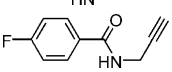
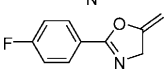
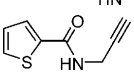
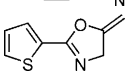
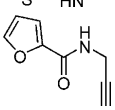
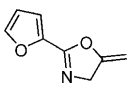
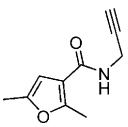
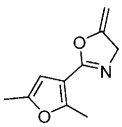
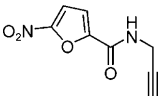
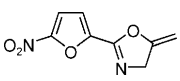
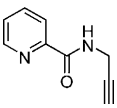
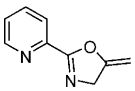
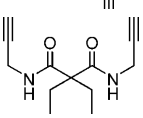
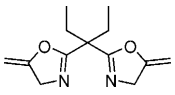
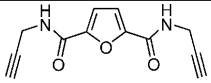
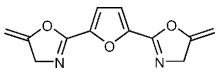
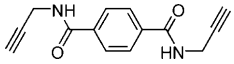
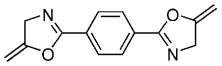
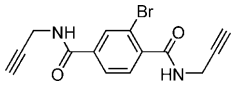
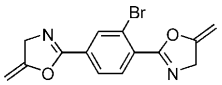
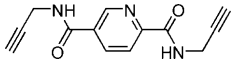
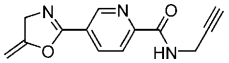
Entry	Starting material	1	Catalyst	Solvent	Time	Product	8	Yield of 8 [%]
1		**o**	2 mol% $[PPh_3Au]NTf_2$	CH_2Cl_2	36 h		**o**	76
2		**a**	2 mol% $[PPh_3Au]NTf_2$	CH_2Cl_2	4 h		**a**	complete conversion[a]
3		**p**	2 mol% $[PPh_3Au]NTf_2$	CH_2Cl_2	34 h		**p**	complete conversion[a]
4		**q**	3 mol% $[PPh_3Au]NTf_2$	CH_2Cl_2	36 h		**q**	8
5		**r**	1 mol% $[PPh^3Au]NTf_2$	CH_2Cl_2	18 h		**r**	95
6		**s**	5 mol% $[PPh_3Au]OTs$	CH_2Cl_2	2 days		**s**	81
7		**t**	5 mol% $[PPh_3Au]OTs$	CH_2Cl_2	2 days		**t**	87
8		**u**	5 mol% $[PPH_3Au]OTs$	CH_2Cl_2	2 days		**u**	81[b]
9		**b**	5 mol% $[PPh_3Au]OTs$	CH_2Cl_2	24 h		**b**	92
10		**v**	1 mol% $[PPh_3Au]NTf_2$	CH_2Cl_2	36 h		**v**	91
11		**w**	1 mol% $[PPh_3Au]NTf_2$	CH_2Cl_2	36 h		**w**	79
12		**x**	4 mol% $[Mes_3Au]NTf_2$	$CHCl_3$	48 h		**x**	74
13		**y**	5 mol% $[PPh_3Au]NTf_2$	$CHCl_3$	3 h		**y**	68
14		**c**	2 mol% $[PPh_3Au]NTf_2$	CH_2Cl_2	34 h		**c**	complete conversion[a]
15		**z**	5 mol% $PPh_3Au]OTs$	CH_2Cl_2	24 h		**z**	67
16		**aa**	5 mol% $[PPh_3Au]OTs$	CH_2Cl_2	24 h		**aa**	82
17		**ab**	5 mol% $[PPh_3Au]OTs$	CH_2Cl_2	4 days		**ab**	30[c]
18		**ac**	5 mol% $[PPh_3Au]OTs$	CH_2Cl_2	6 days		**ac**	37
19		**ad**	5 mol% $[PPh_3Au]OTs$	CH_2Cl_2	24 h		**ad**	80

Table 3. (Continued)

Entry	Starting material	1	Catalyst	Solvent	Time	Product	8	Yield of 8 [%]
20		**ae**	5 mol% $[PPh_3Au]OTs$	CH_2Cl_2	3 days		**ae**	41
21		**f**	3 mol% $[PPh_3Au]NTf_2$	CH_2Cl_2[d]	12 h		**f**	74
22		**g**	2 mol% $[PPh_3Au]NTf_2$	CH_3CN[e]	5 h		**g**	46
23		**h**	5 mol% $[PPh_3Au]NTf_2$	CH_3CN	5 h		**h**	64

[a] Determined by NMR spectroscopic measurements (highly volatile). [b] 2:1 mixture of alkylideneoxazoline/oxazole. [c] Mixture of 56% of starting material, 11% of aromatized oxazole, and 32% of **8ab**. [d] Reaction temperature = 50 °C. [e] Reaction temperature 70 °C.

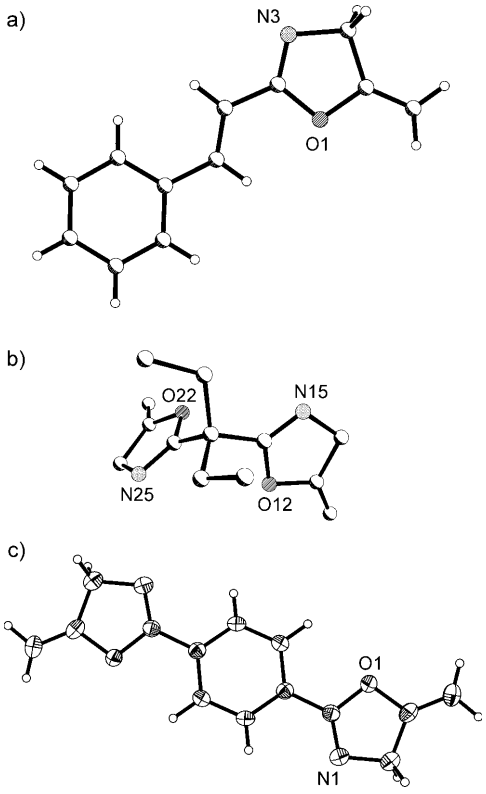
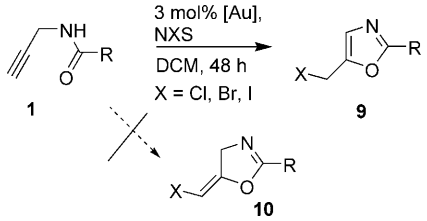


Figure 3. Solid-state structure of methyleneoxazolines **8v** (a), **8ad** (b), and **8f** (c).

Table 4. Formation of halomethyloxazoles **9** from propargylic amides **1**.

Entry	R	Catalyst	NXS[a] (equiv)	Temp. [°C]	9	Yield of 9 [%]
1	$(CH_2)_6CH_3$	$[Ph_3Au]NTf_2$	NCS (5)	40	**a**	7
2	$(CH_2)_6CH_3$	$[Ph_3Au]NTf_2$	NBS (1.5)	20	**b**	9
3	$(CH_2)_6CH_3$	$AuCl_3$	NCS (1.2)	40	**a**	29
4	$(CH_2)_6CH_3$	$AuCl_3$	NBS (1.2)	20	–	–[b]
5	$(CH_2)_6CH_3$	–	NCS (1.2)	40	–	nc[c]
6	$(CH_2)_6CH_3$	–	NBS (1.2)	20	–	–[b]

[a] NBS = *N*-bromosuccinimide, NCS = *N*-chlorosuccinimide. [b] Unselective reaction. [c] nc = no conversion.



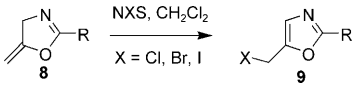
Scheme 5. Formation of halomethyloxazoles **9**.

independent of the oxidation state of the metal catalysts (Table 4, entries 1–4). Control experiments without gold catalyst (Table 4, entries 5 and 6) showed no conversion in the case of *N*-chlorosuccinimide (NCS) and a slow decomposition of the starting material in the case of *N*-bromosuccinimide (NBS).

Not unexpectedly, the isolated methyleneoxazolines **8** could be converted with the electrophilic reagents too, indicating that during the gold-catalyzed version first the vinyl gold species gets proto-demetalated and then in a subsequent uncatalyzed step the final products are formed. Table 5 summarizes the results of the uncatalyzed conversion of the methylenedihydrooxazoles **8**. As for the data in Table 4, the yields of the transformations presented in Table 5 were not satisfying in most cases. Only the adamantyl-substituted substrate (Table 5, entry 4) showed a clean reaction in the case of NBS, while all the other substrates showed significant amounts of byproduct formation during the reaction. Besides the formation of the halogenated product, simple aromatization to oxazoles **2** also took place, leading to inseparable mixtures. Especially in the case of the iodination, substrates turned out to be fairly unstable.

Finally, we used a different halide source, Barluenga's reagent (bis(pyridyl)iodonium(I) tetrafluoroborate (Py_2IBF_4)), which is well known for its ability to activate triple bonds for the attack of different nucleophiles.[20] Table 6 demonstrates the higher effectiveness of this reagent. All the employed substrates showed clean conversion under mild conditions regardless of whether aliphatic (Table 6, entries 1 and 2) or aromatic moieties (Table 6, entries 3–5) were employed, even the alkene in entry 3 was tolerated. As in the

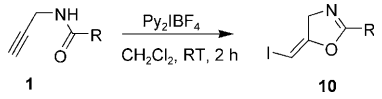
Table 5. Formation of halomethyloxazoles **9** from methylenedihydrooxazoles **8**.



Entry	R	NXS[a] (equiv)	Time	Temp. [°C]	9	Yield of **9** [%]
1		NCS (1.5)	48 h	50	**a**	9[b]
2	$(CH_2)_6CH_3$	NBS (1.5)	48 h	20	**b**	43
3		NIS (1.5)	24 h	20	**c**	49
4		NBS (1.5)	24 h	20	**d**	86
5		NIS (1.5)	24 h	20	**e**	34
6		NCS (3)	48 h	40	**f**	39
7	Ph	NBS (1.5)	24 h	20	**g**	39
8		NIS (1.5)	24 h	20	**h**	34
9		NCS (3)	48 h	40	**i**	16
10		NBS (1.5)	24 h	20	**j**	44
11		NIS (1.5)	24 h	20	–	–[c]
12	*t*Bu	NIS (1.1)	16 h[d]	20	**k**	41
13	Bn	NIS (1.1)	16 h[d]	20	**l**	35
14	thiophenyl	NIS (1.1)	16 h[d]	20	**m**	16

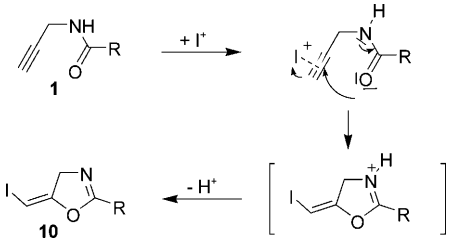
[a] NBS = *N*-bromosuccinimide, NCS = *N*-chlorosuccinimide, NIS = *N*-iodosuccinimide. [b] Inseparable mixture with 23% of the oxazole without halogen. [c] Unselective reaction. [d] The methylenedihydrooxazole was generated in situ, after 16 h NIS was added and the reaction was continued for additional 30 min. (Bn = benzyl).

Table 6. Iodination with Barluenga's reagent.



Entry	R	**10**	Yield of **10** [%]
1	$(CH_2)_6CH_3$	**a**	50
2		**b**	65
3		**c**	71
4	Ph	**d**	69
5		**e**	63

case of the Au^I-catalyzed cyclization, no aromatization to the oxazoles occurred and the iodomethylenedihydrooxazoles **10** could be isolated as pure *E* diastereoisomers. Mechanistically, this transformation shows significant parallels to the gold-catalyzed pathway (Scheme 6). Here the initial step is the coordination of the electrophilic iodine cation, which activates the alkyne triple bond for the *anti* attack of the carbonyl oxygen. The difference lies in the next reaction step, when, after the loss of the proton, the halogen stays in the product; therefore, stoichiometric amounts of the halide source are needed. The *E* configuration of the double bond could be verified by the X-ray crystal structure data of compounds **10c** and **10e** (see Figure 4).[14]



Scheme 6. Formation of iodomethyleneoxazolines **10**.

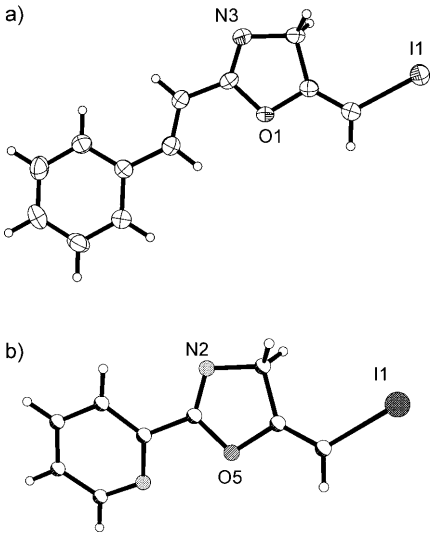


Figure 4. Solid-state structures of iodomethyleneoxazolines **10c** (a) and **10e** (b).

Conclusions

In our study of the gold-catalyzed conversion of propargylic amides we demonstrated that depending on the oxidation state of the gold catalyst, oxazoles (Au^{III} catalysis) or methylenedihydrooxazoles (Au^I catalysis) can reliably be obtained with high chemoselectivities. For both of the applied protocols, a broad range of substrates could be converted, regardless of whether aromatic or aliphatic side chains were used. Furthermore, even substrates with up to three propargylic moieties could be converted in high yields, delivering access to a class of compounds with interesting optical properties. The limitations for both of these methodologies lie in substrates in which electron-deficient substituents decrease the nucleophilicity of the carbonyl oxygen.

Efforts to functionalize the vinylgold intermediates by trapping with *N*-halosuccinimides as electrophiles were not successful; instead a further transformation of the proto-demetalated methylenedihydrooxazoles took place that finally led to halomethyloxazoles. Nevertheless, by using Barluenga's reagent we were able to establish a mild access to the synthetically useful iodomethylenedihydrooxazoles under very mild reaction conditions. The cycloisomerization of substrates with internal alkynes is also under detailed inves-

tigation, preliminary results have just been communicated.[21]

Experimental Section

See the Supporting Information for experimental details.

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