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Gold-Catalyzed Cyclization of Nonterminal Propargylic Amides to Substituted Alkylideneoxazolines and -oxazines

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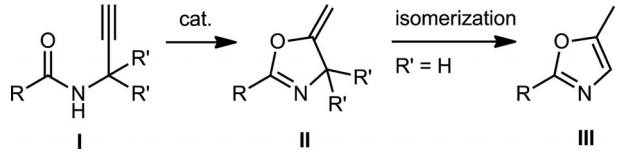
The substrate scope of the gold-catalyzed cyclization of nonterminal propargylic amides to oxazolines and oxazines was investigated. Sixteen alkyl-substituted and 35 aryl-substited substrates were prepared by a very variable route from trimethylsilyl-(TMS-)protected, nonterminal propargylamines. Steric and electronic influences of the substituents on product selectivity were studied. A chloromethyl substituent on the alkyne shows an efficient 1,4-elimination to deliver vinyloxazoles. A second alkynyl group, tethered to the alkyl group at the alkyne, in some cases led to a gold catalysis/Alder–ene domino reaction. With Barluenga's reagent the iodoalkylideneoxazoline can be formed in excellent yield. In contrast to the palladium-catalyzed protocols, the gold-catalyzed conditions for the cyclization of nonterminal propargylic amides are much milder, thus, for example, no special precautions are needed to prevent isomerization of the oxazolines to the aromatic oxazoles.

Introduction

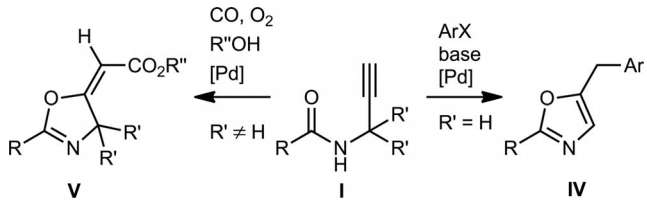
In recent years, the cyclization of propargylic amides **I** to the corresponding methyleneoxazolines **II** and -oxazoles **III** has been a focus of interest (Scheme 1). These transformations have been reported to be catalyzed by strong bases (with very limited functional group tolerance),[1] palladium,[2] copper,[3] silver,[4] and gold.[5] Of these catalysts, the reactions with gold(I) catalysts proceed under the mildest reaction conditions, and thus, the methyleneoxazolines **II** are formed most selectively. For other catalysts, alkyl groups for R′ have often been used to prevent isomerization to the more stable aromatic oxazole **III**.



Scheme 1. Cyclization of the propargylic amides **I** to methyleneoxazolines **II** and isomerization to oxazoles **III**.

Owing to the interesting pharmaceutical properties of 2,5-disubstituted oxazoles as antitumor agents, antifungal agents, herpes simplex virus type 1 (HSV-1) inhibitors, serine threonine phosphate inhibitors, and antibacterials,[6] these catalyzed cyclizations, in particular, gold-catalyzed cyclizations, have found several applications in industrial chemistry.[7]

With palladium, some domino cross-coupling/cyclization reactions are known (Scheme 2). The first step is a cross-coupling reaction with the terminal alkyne of the propargylic amide, which is followed by cyclization to the corresponding oxazole **IV**[2a] or alkylideneoxazoline **V**.[2b]



Scheme 2. Palladium-catalyzed tandem reactions with propargylic amides.

Inspired by these cyclizations of propargylic amides with internal alkynyl groups and following our recent work with methyleneoxazolines,[5e] we now wanted to investigate whether it was possible to cyclize nonterminal propargylic amides with a substituent on the propargyl group. This would allow the synthesis of more complex alkylideneoxazolines, not only those with a methylene group on the heterocyclic ring. But, so far, under the initial reaction conditions, internal alkynes were unreactive.[5a] Herein, we report our results on the gold(I)-catalyzed cyclization of nonterminal propargylic amides.

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Results and Discussion

To have a highly flexible substrate synthesis, we decided to prepare substituted propargylamines instead of modifying terminal propargylic amides **I**. We found that TMS-protected propargylamine[8] was the perfect building block for this approach.

First, we tested alkyl-substituted propargylic amides, which were synthesized by deprotonation of *N*,*N*-bis(trimethylsilyl)propargylamine with *n*-butyllithium and reaction with alkyl iodides (Table 1) to yield the substituted propargylamines **1**. After the reaction with acid chlorides, propargylic amides **2** were obtained in overall yields of 35 to 94% for these two steps.

In the case of compound **2a**, single crystals suitable for an X-ray structure analysis were obtained by recrystallization from dichloromethane/petroleum ether (PE), delivering unambiguous proof for the formation of the non-terminal propargylic amide (Figure 1).[9] This compound was also used for the first catalytic conversion (Scheme 3), which resulted in a mixture of alkylideneoxazoline **3a** and

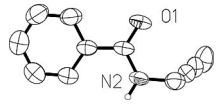
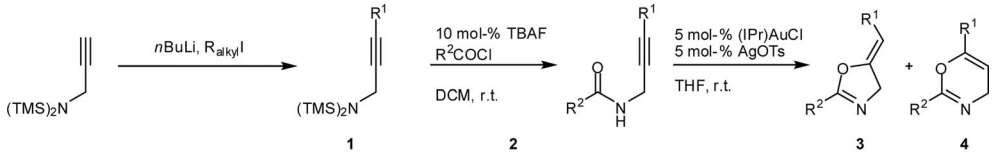
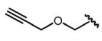


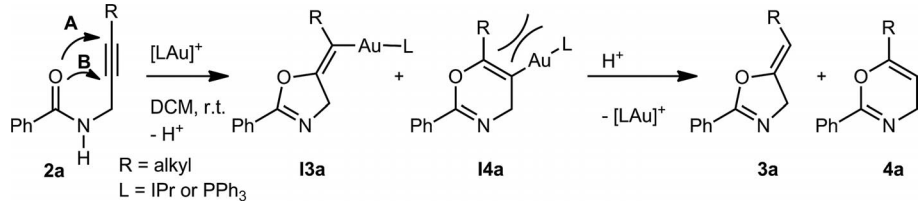
Figure 1. ORTEP representation of substrate **2a**. Ellipsoids are given at the 50% probability level.

Table 1. Synthesis and catalysis of alkyl-substituted propargylic amides (TBAF = tetrabutylammonium fluoride, Ts = *p*-tolylsulfonyl).



Entry	R^1	R^2	Propargylic amides (% yield)	Reaction time	Gold catalysis
1	Me		**2a** (69)	16 h	**3a** (37%), **4a** (35%)
2	Et		**2b** (55)	16 h	**3b** (51%), **4b** (22%)
3	*n*Pr		**2c** (66)	16 h	**3c** (55%), **4c** (15%)
4	*n*Bu		**2d** (56)	16 h	**3d** (57%), **4d** (10%)
5	Me		**2e** (78)	16 h	**3e** (12%), **4e** (19%)
6	Me		**2f** (77)	16 h	–
7	Me		**2g** (63)	16 h	–
8	Me		**2h** (37)	16 h	**3h** (28%)
9	Me		**2i** (68)	16 h	**3i** (38%)
10	*n*Bu		**2j** (81)	16 h	**3j** (78%)
11	CH_2Cl		**2k** (97)[a]	6 d	**5k** (36%)
12	CH_2OCH_3		**2l** (76)	24 h	–
13			**2m** (78)[a]	24 h	**6m** (41%)
14			**2n** (57)	12 h	**3n** (51%), **6n** (15%)
15			**2o** (35)	16 h	**3o** (37%)
16			**2p** (94)	16 h	**3p** (42%)

[a] Reaction with free amine (yield for one step).

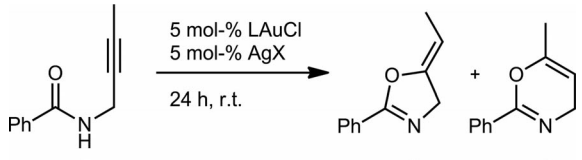


Scheme 3. Different regioselectivities in the cyclization of propargylic amides.

1,3-oxazine **4a**. The oxazine **4a** is formed via a 6-*endo*-*dig* cyclization (path **A**), whereas the oxazoline **3a** originates from the 5-*exo*-*dig* cyclization (path **B**).

For the evaluation of optimal reaction conditions with respect to yield and selectivity, solvent and catalyst screenings were conducted (Table 2). With Ph_3PAuCl/AgOTs as the catalyst, the reaction was performed in CH_3CN, THF, THF/CH_3CN, CH_3NO_2, and CH_2Cl_2 (Table 2, entries 1–5). With CH_3CN and CH_3NO_2 no conversion took place (Table 2, entries 1 and 4). In THF (Table 2, entry 2) the best result was obtained (conversion of 92%), followed by THF/CH_3CN (Table 2, entry 3) with 75% conversion and CH_2Cl_2 (Table 2, entry 5) with 20% conversion. In all cases a mixture of **3a** and **4a** were obtained. With other counterions, such as NTf_2^-[10] or OTf^- (Tf = triflate; Table 2, entries 6 and 7) there was no conversion. The choice of the right solvent and counterion seems to be very crucial for this reaction. Switching to a gold–carbene catalyst [AuCl(IPr)], the conversion in CH_2Cl_2 was only 10% (Table 2, entry 8).

Table 2. Solvent and catalyst screening.



Entry	Gold catalyst	Silver salt	Solvent	Conv.[a] [%]	3a [%]	4a [%]	3a/4a
1	[AuCl(Ph$_3$P)]	AgOTs	CH_3CN	–	–	–	–
2	[AuCl(Ph$_3$P)]	AgOTs	THF	92	38	31	1.22
3	[AuCl(Ph$_3$P)]	AgOTs	CH_3CN/THF	75	31	27	1.15
4	[AuCl(Ph$_3$P)]	AgOTs	CH_3NO_2	–	–	–	–
5	[AuCl(Ph$_3$P)]	AgOTs	CH_2Cl_2	20	4	8	0.50
6	[AuCl(Ph$_3$P)]	$AgNTf_2$	CH_2Cl_2	–	–	–	–
7	[AuCl(Ph$_3$P)]	AgOTf	CH_2Cl_2	–	–	–	–
8	[AuCl(IPr)]	AgOTs	CH_2Cl_2	10	2	7	0.28
9	[AuCl(IPr)]	AgOTs	THF	100	41	37	1.11
10	C1	AgOTs	THF	100	33	48	0.69
11	C2	AgOTs	THF	100	44	35	1.26
12	C3	AgOTs	THF	83	43	20	2.17
13	C4	AgOTs	THF	100	46	28	1.64
14	C5	AgOTs	THF	100	48	26	1.85
15	C6	AgOTs	THF	100	49	32	1.53
16	C7	AgOTs	THF	100	43	37	1.16
17	C8	–[b]	THF	13	3	6	0.50
18	C9	AgOTs	THF	100	44	29	1.51
19	C10	AgOTs	THF	100	39	30	1.30

[a] Conversion and yields determined by GC with dodecane as an internal standard. [b] NTf_2^- preactivated catalyst used.

However, in THF, the conversion reached 100% and yielded a nearly 1:1 mixture of products **3a** and **4a** (Table 2, entry 9). In an attempt to improve the selectivity, we tested a series gold–carbene complexes (Table 2, entries 10–19 and Figure 2), which were recently developed in Echavarren's and our group.[11] In almost all cases, using THF as the solvent, resulted in 100% conversion. Only the isocyanide complex **C3** gave a slightly lower conversion (83%), presumably due to a lower catalyst stability. Even worse was **C8**, an NTf_2^- preactivated catalyst, with only 13% conversion. Here again the influence of the counterion is visible.

With all of these catalysts, the selectivity was not shifted towards one of the products. The best selectivity was observed with **C1** (Table 2, entry 10), an open carbene, with a product ratio of **3a/4a** = 0.68; **C3** (Table 2, entry 12), an isocyanide complex, with a ratio of **3a/4a** = 2.17; and **C5** (Table 2, entry 14), a very bulky closed carbene, with a ratio of **3a/4a** = 1.83. It is also interesting that at low conversions (Table 2, entries 5, 8, and 17) product **4a** is favored, whereas higher conversions, in almost all cases, lead to a slight preference for product **3a**. Control experiments with only AgOTs as the catalyst gave no conversion. With these data, we decided to use [AuCl(IPr)] and AgOTs in THF as the catalyst system for other substrates.

With suitable reaction conditions in hand, we carried out the cycloisomerization with a series of substrates (Table 1) to test the scope of the reaction. First, we changed the chain length R^1 at the alkyne, keeping Ph as the R^2 moiety (Table 1, entries 1–4). With a methyl group, we obtained a nearly 1:1 mixture of **3a**, with 37% yield, and **4a**, with 35% yield. Therefore, the isolated yield correlates to the yield determined by GC in the catalyst screening. Extending the chain length to ethyl, 51% of **3b** and 22% of **4b** were isolated. *n*-Propyl yielded 55% of **3c** and 15% of **4c**. As longest chain in this series *n*-butyl was tested and yielded 57% of **3d** and 10% of **4d**. The longer the chain at the alkyne, the more oxazoline **3** is favored as the product. This can be explained by steric hindrance between the alkyl chain and catalyst in the intermediates **I3a** and **I4a** (Scheme 3), which have been recently studied in our group.[12]

Next, we changed the R^2 moiety and kept the methyl group as R^1. With the 4-bromophenyl substituent, the yields dropped to 12% for **3e** and 19% for **4e** (Table 1, entry 5). With styryl and 2-furyl as R^2 no reaction occurred (Table 1, entries 6 and 7). 2,5-Dimethylfuryl yielded 28% for **3h**. Product **4h** could be detected, but was so sensitive that no clean NMR spectrum could be measured (Table 1, entry 8). When using an adamantyl substituent, only oxaz-

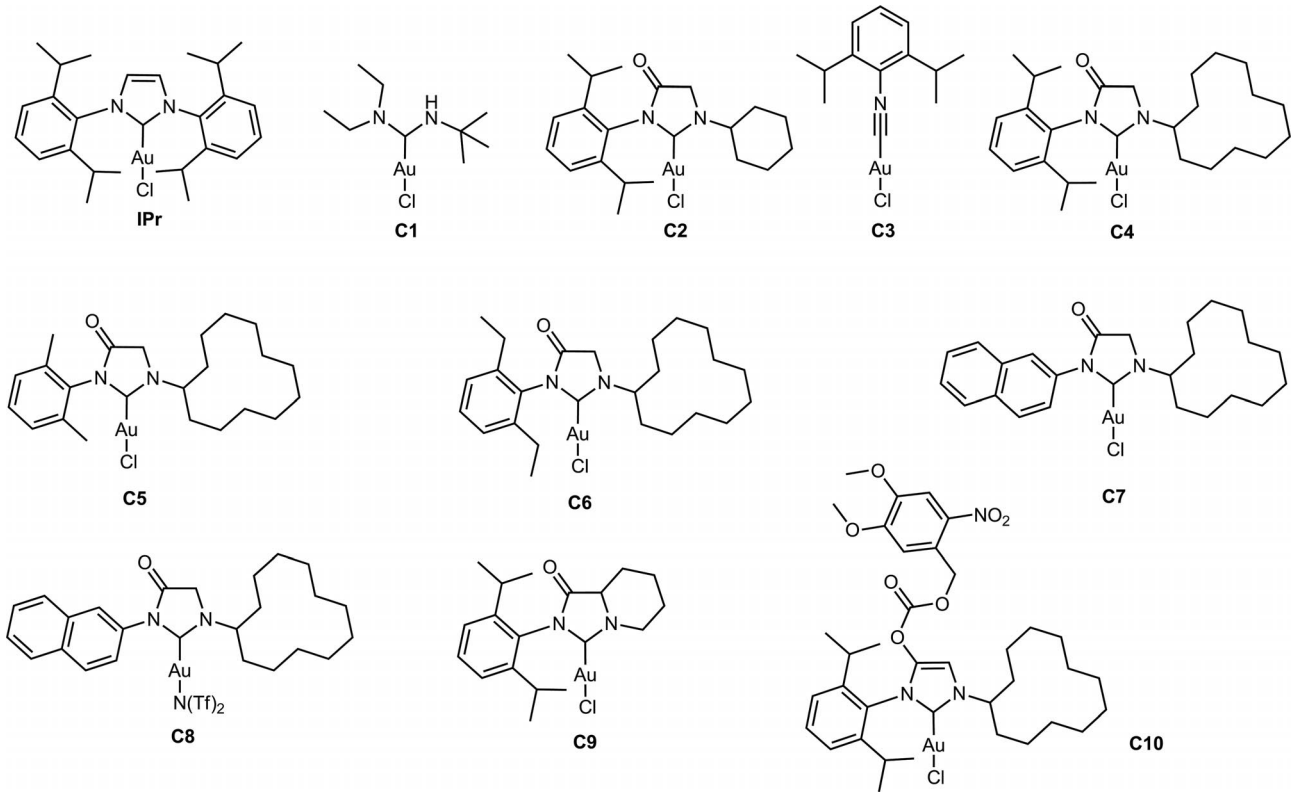
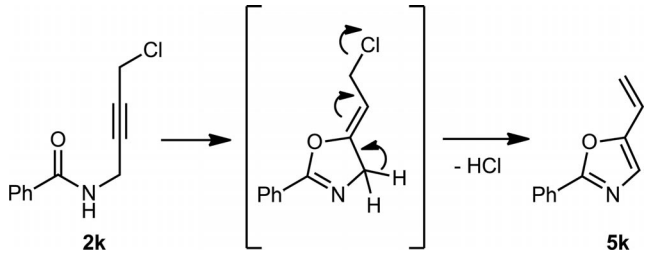


Figure 2. Structures of the catalysts used for the screening (Table 2).

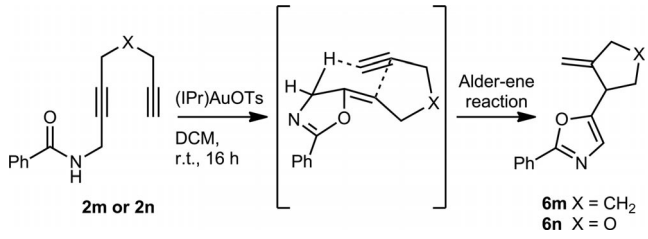
oline **3i** was obtained (38% yield). With adamantyl we also tried an *n*-butyl chain for R^1, which yielded 78% of oxazoline **3j** (Table 1, entry 10).

Next, we tested some functionalized R^1 groups and kept phenyl as the R^2 moiety. With a chloromethyl group vinyl oxazole **5k** was obtained in 36% yield (Table 1, entry 11). In this case, the yield was limited by the inhibition of the catalyst from the emerging HCl (Scheme 4). This 1,4-elimination is promoted by the formation of the aromatic oxazole ring system in **5k**.



Scheme 4. Formation of product **5k**.

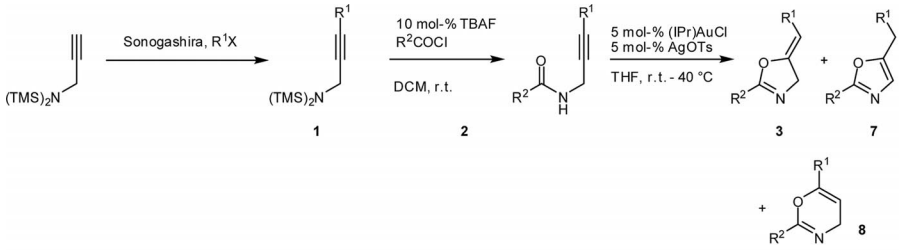
With a methyoxymethyl group, no product was isolated (Table 1, entry 12). The starting material decomposed. With a pentynyl group, product **6m** was isolated in 41% yield as the only product. This product is formed by an Alder–ene reaction[13] of the oxazoline (Scheme 5). For the propargyloxy methyl moiety, oxazoline **3n** was obtained in 51% yield, which slowly reacts through an Alder–ene reaction to give **6n**, isolated in 15% yield (Table 1, entry 14, and Scheme 5). The low yields of the Alder–ene reactions probably originate from the absence of a Thorpe–Ingold effect in the tether. Thus, the conformation needed for the second cyclization, is disfavored. When the intermediate alkylideneoxazoline was isolated after incomplete conversion, the Alder–ene reaction also proceeded in the absence of the gold catalyst. Elongation of the chain to hexyl yielded only **3o**, which did not give an Alder–ene reaction. A pentene group produced oxazoline **3p** in 42% yield.



Scheme 5. Formation of products **6m** and **6n** by Alder–ene reaction.

After testing the alkyl-substituted propargylic amides, we were interested in the reactivity of the aryl-substituted derivatives (Table 3). These aryl-substituted substrates were synthesized through Sonogashira coupling of TMS-protected propargylamine and subsequent reaction with acid chlorides to obtain the amides **2q**–**2ay** in 18–80% yield over two steps (Table 3). We decided to use four different R^2 groups, namely, phenyl, 2-furyl, benzyl, and *tert*-butyl. All reactions were carried out at 40 °C in CH_2Cl_2 with [Au(IPr)(OTs)] as the catalyst.

Table 3. Synthesis and catalysis of aryl-substituted propargylic amides.



Entry	R^1	R^2	Products **2** (% yield)	Conditions for the gold catalysis	Products of the gold-catalyzed conversion
1			**2q** (67)	12 h, r.t.	**3q** (91%)
2			**2r** (60)	5 d, 40 °C	–
3			**2s** (61)	5 d, 40 °C	–
4			**2t** (83)	12 h, r.t.	**3t** (84%)
5			**2u** (26)	5 d, 40 °C	–
6			**2v** (29)	5 d, 40 °C	–
7			**2w** (18)	5 d, 40 °C	–
8			**2x** (29)	5 d, 40 °C	–
9			**2y** (55)	5 d, 40 °C	–
10			**2z** (40)	5 d, 40 °C	–
11			**2aa** (28)	5 d, 40 °C	–
12			**2ab** (39)	5 d, 40 °C	–
13			**2ac** (40)	12 h, r.t.	**7ac** (92%)
14			**2ad** (80)	3 d, 40 °C	**7ad** (39%)
15			**2ae** (40)	36 h, 40 °C	**3ae** (56%)[a]
16			**2ae** (40)	5 d, 40 °C	**7ae** (69%)[a]
17			**2af** (80)	12 h, 40 °C	**3af** (90%)
18			**2ag** (73)	16 h, 40 °C	**3ag** (90%)
19			**2ah** (73)	5 d, 40 °C	–
20			**2ai** (54)	5 d, 40 °C	–
21			**2aj** (73)	16 h, 40 °C	**3aj** (95%)
22			**2ak** (63)	16 h, 40 °C	**3ak** (86%)
23			**2al** (63)	5 d, 40 °C	–
24			**2am** (54)	5 d, 40 °C	–
25			**2an** (73)	16 h, 40 °C	**3an** (81%)
26			**2ao** (54)	16 h, 40 °C	**7ao** (67%)
27			**2ap** (58)	5 d, 40 °C	–
28			**2aq** (59)	16 h, 40 °C	**7aq** (79%)

Table 3. (*Continued*).

29		**2ar** (53)	12 h, 40 °C	**3ar** (93%)
30		**2as** (51)	3 d, 40 °C	**3as** (27%)
31		**2at** (28)	5 d, 40 °C	–
32		**2au** (47)	12 h, 40 °C	**3au** (80%)
33		**2av** (57)	12 h, 40 °C	**3av** (42%), **7av** (16%), **8av** (16%)[b]
34		**2av** (57)	5 d, 40 °C	**3av** (36%), **7av** (25%), **8av** (5%)[b]
35		**2aw** (55)	36 h, 40 °C	**3aw** (60%), **7aw** (18%)[b]
36		**2aw** (55)	5 d, 40 °C	**3aw** (14%), **7aw** (53%)[b]
37		**2ax** (53)	12 h, 40 °C	**3ax** (73%)
38		**2ay** (45)	12 h, 40 °C	**3ay** (94%)

[a] Inseparable from the unreacted starting material. [b] Inseparable mixture of products.

For substrates **2z**, **2ar**, **2as**, and **2at** single crystals suitable for X-ray structure analysis were obtained by recrystallization from CH_2Cl_2/PE (Figure 3).[9] The structures shown give unambiguous proof for the formation of aryl-coupled propargylic amides.

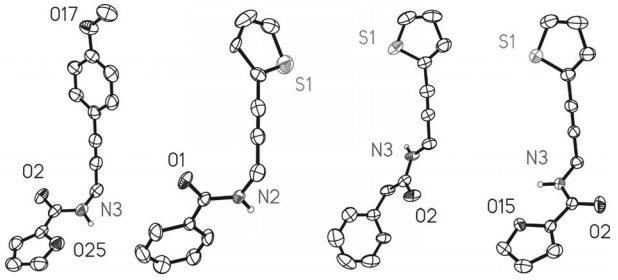


Figure 3. ORTEP representations of compounds **2z**, **2ar**, **2as**, and **2at** (from left to right). Ellipsoids are given at the 50% probability level.

First, we tested phenyl as R^1, which delivers (with phenyl as R^2) an excellent yield of 91% for **3q** (Table 3, entry 1). For this compound, we were able to obtain single crystals suitable for X-ray structure analysis by recrystallization from CH_2Cl_2/PE (Figure 4).[9] The structure shows the oxidized form of the oxazoline; a carbonyl group forms at the activated position between the two aromatic rings by autoxidation due to air contact during crystallization. With 2-furyl and benzyl as R^2, no conversion occurred (Table 3, entries 2 and 3). With *tert*-butyl, a very good yield of 84% was obtained for **3t** (Table 3, entry 4).

For 1-naphthyl (Table 3, entries 5–8) and *p*-methoxyphenyl (Table 3, entries 9–12) as R^1, no conversion was observed in any combination with R^2. In case of 1-naphthyl, steric hindrance with the catalyst in the intermediate is so large that no reaction occurs (Scheme 3). For the *p*-methoxyphenyl substituent, the electron-donating effect of the methoxy group (+M) causes increased electron density

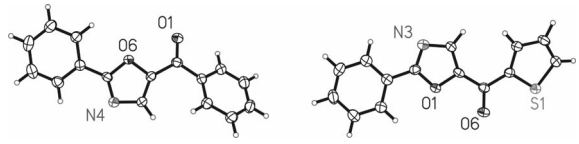


Figure 4. Solid-state molecular structures of oxidised **3q** and **3ar**. Ellipsoids are given at the 50% probability level.

at the alkyne, thus the oxygen atom of the amide group is not able to attack as a nucleophile at the alkyne (Figure 5).

When testing the *p*-nitrophenyl substituent, some product could be isolated for all examples. With a phenyl group as R^2, an excellent yield of 92% for **7ac** was obtained (Table 3, entry 13). A 2-furyl moiety yielded 39% of oxazole **7ad** (Table 3, entry 14). With benzyl oxazoline, product **3ae** was obtained in 56% after 36 h in a mixture with the starting material (Table 3, entry 15). In attempt to increase conversion and yield, the reaction was performed again with a prolonged reaction time of 5 d (Table 3, entry 16); this led to a slight increase in the yield of oxazole **7ae**. The longer reaction time had little influence on the yield, but led to complete isomerization of oxazoline **3ae** to oxazole **7ae**. With a *tert*-butyl group, the reaction produced an excellent yield of 90% for **3af** (Table 3, entry 17).

p-Cyanophenyl, which was less electron-withdrawing than *p*-nitrophenyl, was coupled next. With a phenyl moiety as R^2, product **3ag** was produced in an excellent yield of 90% (Table 3, entry 18). With 2-furyl and benzyl, no conversion was observed (Table 3, entries 19 and 20). A *tert*-butyl moiety produced **3aj** in an excellent yield of 95% (Table 3, entry 21).

Using even less electron-withdrawing *p*-formylphenyl as R^1 produced (with phenyl as R^2) a very good yield of 86% for **3ak** (Table 3, entry 22). Here, there was also no conversion with 2-furyl and benzyl moieties (Table 3, entries 23 and 24). With *tert*-butyl, product **3an** was obtained in a very good yield of 81% (Table 3, entry 25).

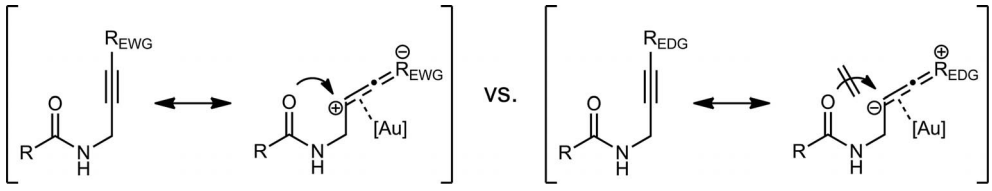
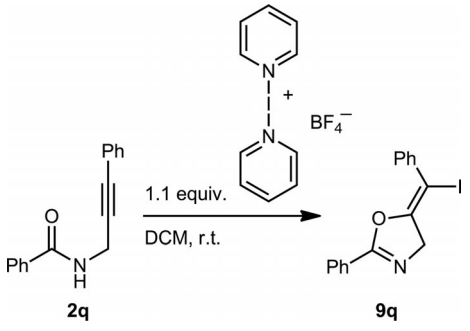


Figure 5. Effect of electron-withdrawing (EWG) and -donating (EDG) groups on the cyclization.

Then, we switched to heteroaromatic groups as R^1, starting with 2-pyridyl. With a phenyl moiety as R^2, oxazole **7ao** was obtained in 67% yield (Table 3, entry 26). The 2-furyl moiety gave no conversion (Table 3, entry 27). A very good yield of 79% for oxazole **7aq** could be reached with the *tert*-butyl moiety (Table 3, entry 28). This is the only example in which a substrate with *tert*-butyl produced oxazole instead of oxazoline.

With 2-thiopenyl as the alkyne and phenyl in the R^2 position, the reaction gave an excellent 93% yield for oxazoline **3ar** (Table 3, entry 29). For this compound, a single crystal suitable for X-ray structure analysis was obtained by recrystallization from CH_2Cl_2/PE (Figure 4).[9] As for **3q**, the structure shown is the oxidized form of the oxazoline. With the 2-furyl group, after 3 d, 27% yield of **3as** was obtained (Table 3, entry 30). The benzyl moiety gave no conversion and *tert*-butyl yielded 80% of **3au** (Table 3, entries 31 and 32).

Coupling with 5-bromofurfural delivered the highest density of functional groups of all substrates tested. With phenyl as R^2, after 12 h the reaction gave a mixture of 42% oxazoline **3av**, 16% oxazole **7av**, and 16% of oxazine **8av** (Table 3, entry 33). This is the only substrate with an aryl substituent at the alkyne that produces oxazine. When the reaction was carried out for an elongated reaction time of 5 d, 36% of oxazoline **3av**, 25% of oxazole **7av**, and 5% of oxazine **8av** were obtained (Table 3, entry 34). Here the longer reaction time also caused only a slight increase in yield, but a massive increase in isomerization. After 36 h, the 2-furyl group delivered oxazoline **3aw** in 60% yield and oxazole **7aw** in 18% yield (Table 3, entry 35). A prolonged reaction time of 5 d isomerized most of the oxazoline **3aw** (14% yield) into the oxazole **7aw** (53% yield; Table 3, entry 36). With the benzyl group, 73% yield oxazoline **3ax** was obtained, whereas the *tert*-butyl group produced again an excellent yield of 94% for oxazoline **3ay** (Table 3, entries 37 and 38).



Scheme 6. Reaction of substrate **2q** with Barluenga's reagent to the corresponding iodooxazoline **9q**.

We then tested the reaction with Barluenga's reagent, $[Py_2I][BF_4]$,[14,15] for substrate **2q** (Scheme 6). With terminal propargylic amides, this conversion proceeded readily.[5d] Nonterminal substrate **2q** also reacted smoothly to give iodooxazoline **9q** in 94% yield. Testing the scope of this transformation is part of our ongoing research.

Conclusions

We have shown that the gold-catalyzed cyclization of propargyl amides is not limited to terminal alkynes. We were able to cyclize a series of substrates with alkyl, functionalized alkyl (Table 1), and aryl groups (Table 3) on the alkyne and again increased the scope of this fascinating reaction. We have also explored the limitations of this method, which could be useful when planning further applications. Furthermore, the intermolecular Alder–ene reaction of the oxazoline products (Scheme 5) delivered interesting products and is part of our ongoing studies. Further investigations should focus on using the Alder–ene reaction in an intermolecular manner.

Experimental Section

General Procedure A (GP A). Alkylation of *N*,*N*-Bis(trimethylsilyl)-propargylamine: In a flame-dried Schlenk flask under a nitrogen atmosphere, *N*,*N*-bis(trimethylsilyl)propargylamine[8] (1 equiv.) dissolved in THF was added. The reaction mixture was cooled to –78 °C and *n*BuLi (1.2 equiv.) was added dropwise. Afterwards the reaction mixture was warmed to room temperature and stirred for 30 min. The alkyl iodide (1.0 equiv.) was added. The reaction mixture was stirred at 40 °C for 2 d. The reaction progress was observed by GC/MS measurements. The reaction mixture was filtered through a small column of basic alumina and washed twice with PE/EA/DEA (200 mL, 10:1:0,1). After removal of the solvent in vacuo, the crude product was used in subsequent reactions without further purification.

General Procedure B (GP B). Arylation of *N*,*N*-Bis(trimethylsilyl)-propargylamine by Sonogashira Cross Coupling: In a flame-dried Schlenk flask under a nitrogen atmosphere, the aryl halide (1.2 equiv.) and *N*,*N*-bis(trimethylsilyl)propargylamine (1 equiv.) were dissolved in TEA or in a mixture of TEA/THF (1:1; for insoluble aryl halides). The reaction mixture was degassed three times and $[PdCl_2(Ph_3P)_2]$ (2 mol-%) was added. After 10 min, CuI (1 mol-%) was added. The reaction mixture was stirred for the indicated time and temperature. After complete conversion of *N*,*N*-

bis(trimethylsilyl)propargylamine, the reaction mixture was filtered through a small column of basic alumina and washed twice with PE/EA/DEA (200 mL, 10:1:0.1). After removal of the solvent in vacuo, the crude product was used in subsequent reactions without further purification.

General Procedure C (GP C). Synthesis of Carboxamides with *N*,*N*-Bis(trimethylsilyl)propargylamines: In a flame-dried Schlenk flask under a nitrogen atmosphere, *N*,*N*-bis(trimethylsilyl)propargylamine (1 equiv.) was dissolved in CH_2Cl_2. Acid chloride (1.1 equiv.) and TBAF (10 mol-%) were added. The reaction was stirred at room temp. overnight. After that the crude product was absorbed on Celite by concentration of the reaction mixture and Celite 545 in vacuo. The reaction mixture was purified by flash chromatography on silica.

General Procedure D (GP D). Gold Catalysis: In a dry Schlenk flask or a dry sealed vial, the gold catalyst (5 mol-%) and the silver salt (5 mol-%) were dissolved in the indicated solvent and stirred for 1 h. *N*-Propargylcarboxyamide (1 equiv.) was added and the reaction was stirred at the indicated temperature for the indicated time. The reaction progress was monitored by TLC or GC/MS measurements. After that the crude product was absorbed on Celite by concentration of the reaction mixture and Celite 545 in vacuo. The reaction mixture was purified by flash chromatography on silica.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data for compounds **1a**–**1r**, **2**a–**2ay**, **3a**–**4e**, **4a**–**4e**, **3h**, **3j**, **5k**, **6m**, **6n**, **3o**–**3q**, **3t**, **7ac**, **7ae**, **3ae**, **7ag**, **3ag**, **7ak**, **3af**, **3aj**, **3ak**, **3an**, **7ao**, **7aq**, **2ar**, **2as**, **2ak**, **7av**, **8av**, **7aw**, **3ax**, **3ay**, **9q**.

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[1] a) B. M. Nilsson, U. Hacksell, *J. Heterocycl. Chem.* **1989**, *26*, 269–275; b) B. M. Nilsson, H. M. Vargas, B. Ringdahl, U. Hacksell, *J. Med. Chem.* **1992**, *35*, 285–294.

[2] a) A. Arcadi, S. Cacchi, L. Cascia, G. Fabrizi, F. Marinelli, *Org. Lett.* **2001**, *3*, 2501–2504; b) A. Bacchi, M. Costa, B. Gabriele, G. Pelizzi, G. Salerno, *J. Org. Chem.* **2002**, *67*, 4450–4457; c) A. Bacchi, M. Costa, N. Della Cà, B. Gabriele, G. Salerno, S. Cassoni, *J. Org. Chem.* **2005**, *70*, 4971–4979; d) E. M. Beccalli, E. Borsini, G. Broggini, G. Palmisano, S. Sottocornola, *J. Org. Chem.* **2008**, *73*, 4746–4749.

[3] C. Jin, J. P. Burgess, J. A. Kepler, C. E. Cook, *Org. Lett.* **2007**, *9*, 1887–1890.

[4] M. Harmata, C. Huang, *Synlett* **2008**, 1399–1401.

[5] a) A. S. K. Hashmi, J. P. Weyrauch, W. Frey, J. W. Bats, *Org. Lett.* **2004**, *6*, 4391–4394; b) M. D. Milton, Y. Inada, Y. Nishibayashi, S. Uemura, *Chem. Commun.* **2004**, 2712–2713; c) A. S. K. Hashmi, M. Rudolph, S. Schymura, J. Visus, W. Frey, *Eur. J. Org. Chem.* **2006**, 4905–4909; d) D. Aguilar, M. Contel, R. Navarro, T. Soler, E. P. Urriolabeitia, *J. Organomet. Chem.* **2008**, *694*, 486–493; e) J. P. Weyrauch, A. S. K. Hashmi, A. M. Schuster, T. Hengst, S. Schetter, A. Littmann, M. Rudolph, M. Hamzic, J. Visus, F. Rominger, W. Frey, J. W. Bats, *Chem. Eur. J.* **2010**, *16*, 956–963.

[6] a) D. C. Palmer, S. Venkatraman, in: *The Chemistry of Heterocyclic Compounds*, A Series of Monographs, *Oxazoles: Synthesis Reactions and Spectroscopy*, Part A (Ed.: D. C. Palmer), Wiley, New York, **2003**; b) S. Lang-Fugmann, in: *Methoden der Organischen Chemie* (Ed.: E. Schaumann), Houben-Weyl, Thieme, Stuttgart, Germany, **1993**; c) R. Lakham, B. Ternai, *Adv. Heterocycl. Chem.* **1974**, *17*, 99–211; d) G. J. Pattenden, *Heterocycl. Chem.* **1992**, *29*, 607–618.

[7] a) S. Zemolka, B. Nolte, K. Linz, D. J. Saunders, W. Schroeder, W. Englberger, F. Theil, H. Schick, J. Kaufmann, J. Gebauer, H. Sonnenschein, WO 2009118174A1, **2009** [*Chem. Abstr.* **2009**, 151, 425530]; b) S. P. Brown, P. Dransfield, J. B. Houze, J. Liu, J. Liu, Z. Ma, J. C. Medina, V. Pattaropong, M. J. Schmitt, R. Sharma, Y. Wang, WO 2008030618A1, **2008**, [*Chem. Abstr.* **2008**, 148, 355798]; c) H. Priepke, G. Dahmann, K. Gerlach, R. Pfau, W. Wienen, A. Schuler-Metz, S. Handschuh, H. Nar, WO2007003536A1, **2007** [*Chem. Abstr.* **2007**, 146, 142521]; d) M. Akerman, J. Houze, D. C. H. Lin, J. Liu, J. Luo, J. C. Medina, W. Qiu, J. D. Reagan, R. Sharma, S. J. Shuttleworth, Y. Sun, J. Zhang, L. Zhu, WO2005086661A2, **2005** [*Chem. Abstr.* **2005**, 143, 326090]; e) D. Dorsch, L. T. Burgdorf, R. Gericke, N. Beier, W. Mederski, W. WO 2005123688A2, **2005** [*Chem. Abstr.* **2005**, 144, 69837]; f) D. Dorsch, O. Schadt, A. Blaukat, F. Stieber, F. WO 2008017361A2, **2008** [*Chem. Abstr.* **2008**, 148, 190536].

[8] R. J. P. Corriu, V. Huynh, J. Iqbal, J. J. E. Moreau, C. Vernhet, *Tetrahedron* **1992**, *48*, 6231–6244.

[9] CCDC-808210 (for **2a**), -808211 (for **2z**), -808212 (for **2ar**), -808213 (for **2as**), -808214 (for **2at**), -808215 (for **3q**) and -808216 (for **3ar**) contain 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.

[10] N. Mezailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133–4136.

[11] a) C. Bartolomé, Z. Ramiro, D. García-Cuadrado, P. Pérez-Galán, M. Raducan, C. Bour, A. M. Echavarren, P. Espinet, *Organometallics* **2010**, *29*, 951–956; b) A. S. K. Hashmi, T. Hengst, C. Lothschütz, F. Rominger, *Adv. Synth. Catal.* **2010**, *352*, 1315–1337; c) A. S. K. Hashmi, C. Lothschütz, C. Böhling, T. Hengst, C. Hubbert, F. Rominger, *Adv. Synth. Catal.* **2010**, *352*, 3001–3012.

[12] A. S. K. Hashmi, A. M. Schuster, F. Rominger, *Angew. Chem.* **2009**, *121*, 8396–8398; *Angew. Chem. Int. Ed.* **2009**, *48*, 8247–8249.

[13] K. Alder, F. Pascher, A. Schmitz, *Ber. Dtsch. Chem. Ges.* **1943**, *76*, 27–53.

[14] For representative examples of the use of Barluenga's reagent, see: a) J. Barluenga, M. A. Rodríguez, J. M. González, P. J. Campos, *Tetrahedron Lett.* **1990**, *31*, 4207–4210; b) J. Barluenga, H. Vázquez-Villa, A. Ballesteros, J. M. González, *J. Am. Chem. Soc.* **2003**, *125*, 9028–9029; c) J. Barluenga, M. Trincado, M. Marco-Arias, A. Ballesteros, E. Rubido, J. M. González, *Chem. Commun.* **2005**, 2008–2010; for a review, see: J. Barluenga, *Pure Appl. Chem.* **1999**, *71*, 431–436.

[15] For investigations on halogenation reactions in gold catalysis, see: a) A. Buzas, F. Gagosz, *Org. Lett.* **2006**, *8*, 515–518; b) A. Buzas, F. Gagosz, *Synlett* **2006**, 2727–2730; c) A. Buzas, F. Istrate, F. Gagosz, *Org. Lett.* **2006**, *8*, 1958–2006; d) S. F. Kirsch, *Angew. Chem.* **2007**, *119*, 2360–2363; *Angew. Chem. Int. Ed.* **2007**, *46*, 2310–2313; e) L. Zhang, *Org. Lett.* **2007**, *9*, 2147–2150; f) B. Crone, S. F. Kirsch, *J. Org. Chem.* **2007**, *72*, 5435–5438; g) M. Yu, G. Zhang, L. Zhang, *Org. Lett.* **2007**, *9*, 2147–2150; for a study of this elemental step, see: h) A. S. K. Hashmi, T. Dondeti Ramamurthi, F. Rominger, *J. Organomet. Chem.* **2009**, *694*, 592–597; i) A. S. K. Hashmi, T. D. Ramamurthi, M. H. Todd, A. S.-K. Tsang, K. Graf, *Aust. J. Chem.* **2010**, *63*, 1619–1626.

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