JOC*Note*

Gold-Catalyzed Synthesis of Alkylidene 2-Oxazolidinones and 1,3-Oxazin-2-ones

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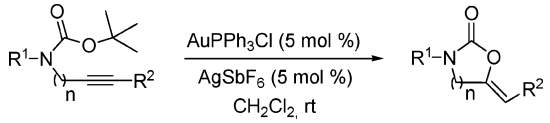

N-Boc-protected alkynylamines are converted into the corresponding alkylidene 2-oxazolidinones or 2-oxazinones under very mild reaction conditions in the presence of 1−5 mol % of a cationic Au(I) complex. The scope of the reaction is very general, providing the cyclic carbamates in high yield regardless of the substitution at nitrogen and alkyne terminus.

2-Oxazolidinones and 2-oxazinones are very important structural motifs in organic synthesis. Part of this interest derives from their broad use as chiral auxiliaries and amino alcohol synthons in organic transformations.[1,2] In addition, appropriately substituted natural or synthetic oxazolidinones and oxazinones have shown outstanding biological properties.[3] For instance, *N*-aryl oxazolidinones functionalized at the C-5 position have recently attracted much attention as a new class of completely synthetic antimicrobial agents, active against multidrug-resistant gram-positive organisms.[4]

Although there are a variety of interesting methods for the synthesis of oxazolidinones and oxazinones from different types of starting materials,[5] such as amino alcohol derivatives, alkenyl amides and carbamates, epoxides, or aziridines, the development of practical and efficient methods for the preparation of these target cyclic carbamates, especially those functionalized with groups sensitive to acid or basic conditions, continue to be of great interest.

As a result of the excellent ability of late transition metals to activate alkynes toward nucleophilic attack, numerous novel catalytic cyclizations based on this strategy have been developed in the last years.[6] Especially Au(I)- and Au(III)-catalyzed processes[7] are emerging as an extremely useful tool for the formation of C−C,[8] C−N,[9] and C−O[10] bonds from alkynes. Taking into account these precedents and the known Au(III) cyclization of propargylic amides to oxazoles,[10e] we envisaged that 5-alkylidene 2-oxazolidinones and 6-alkylidene 2-oxazinones could be directly prepared by gold-catalyzed cyclization of the readily available alkynyl carbamates.[11]

To test this assumption, we selected as the model substrate the BOC-protected *N*-aryl propargylamine **1**.[12] We were pleased

(1) For some reviews on oxazolidinones in asymmetric synthesis, see: (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835−876. (b) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23−29. For a recent example, see: (c) Hogan, P. C.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 15386−15387.

(2) For the use of 2-oxazinones as synthetic intermediates, see for instance: (a) Abbas, T. R.; Cadogan, J. I. G.; Doyle, A.; Gosney, I.; Hodgson, P. K. G.; Howells, G. E.; Hulme, A. N.; Parsons, S.; Sadler, I. H. *Tetrahedron Lett.* **1997**, *38*, 4917−4920. For the synthesis of 1,3-amino alcohols, see: (b) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Chem. Lett.* **1988**, 87−90. For biological interest of 1,3-amino alcohols, see: (c) Benedetti, F.; Norbedo, S. *Chem. Commun.* **2001**, 203−204 and references therein.

(3) Oxazolidinones: (a) Kim, J. D.; Kim, I. S.; Jin, C. H.; Zee, O. P.; Jung, Y. J. *Org. Lett.* **2005**, *7*, 4025−4028. (b) Mai, A.; Artico, M.; Esposito, M.; Sbardella, G.; Massa, S.; Befani, O.; Turini, P.; Giovannini, V.; Mondovi, B. *J. Med. Chem.* **2002**, *45*, 1180−1183. Oxazinones: (c) Van Dang, G.; Rode, B. M.; Stuppner, H. *Eur. J. Pharm. Sci.* **1994**, *2*, 331−50. (d) Sakai, K.; Ichikawa, T.; Yamada, K.; Yamashita, M.; Tanimoto, M.; Hikita, A.; Ijuin, Y.; Kondo, K. *J. Nat. Prod.* **1988**, *51*, 845−850.

(4) (a) Das, J.; Rao, C. V. L.; Sastry, T. V. R. S.; Roshaiah, M.; Sankar, P. G.; Khadeer, A.; Kumar, M. S.; Mallik, A.; Selvakumar, N.; Iqbal, J.; Trehan, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 337−345. (b) Cui, Y.; Dang, Y.; Yang, Y.; Zhang, S.; Ji, R. *Eur. J. Med. Chem.* **2005**, *40*, 209−214. (c) Bozdogan, B.; Appelbaum, P. C. *Int. J. Antimicrob. Agents* **2004**, *23*, 113−119. (d) Arora, V.; Salunkhe, M. M.; Sinha, N.; Sinha, R. K.; Jain, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4647−4650. (e) Diekema, D. J.; Jones, R. N. *Drugs* **2000**, *59*, 7−16.

(5) For recent references, see: (a) Hein, J. E.; Geary, L. M.; Jaworski, A. A.; Hultin, P. G. *J. Org. Chem.* **2005**, *70*, 9940−9946. (b) Osa, Y.; Hikima, Y.; Sato, Y.; Takino, K.; Ida, Y.; Hirono, S.; Nagase, H. *J. Org. Chem.* **2005**, *70*, 5737−5740. (c) Ghosh, A.; Sieser, J. E.; Riou, M.; Cai, W.; Rivera-Ruiz, L. *Org. Lett.* **2003**, *5*, 2207−2210. (d) Sim, T. B.; Kang, S. H.; Lee, K. S.; Lee, W. K.; Yun, H.; Dong, Y.; Ha, H.-J. *J. Org. Chem.* **2003**, *68*, 104−108. (e) Shi, M.; Shen, Y.-M. *J. Org. Chem.* **2002**, *67*, 16. (f) Lei, A.; Liu, G.; Lu, X. *J. Org. Chem.* **2002**, *67*, 974−980. (g) Nicolau, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 625−628.

(6) For recent reviews on the metal-mediated electrophilic activation of alkynes, see: (a) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328−2334. (b) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431−436. (c) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215−236. (d) Méndez, M.; Mamane, V.; Fürstner, A. *Chemtracts* **2003**, *16*, 397−425. (e) Méndez, M.; Echavarren, A. M. *Eur. J. Org. Chem.* **2002**, 15−28.

(7) For recent reviews on gold-catalyzed reactions, see: (a) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990−6993. (b) Hashmi, A. S. K. *Gold Bull. (London)* **2004**, *37*, 51−65. (c) Dyker, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4237−4239.

(8) For very recent references, see: (a) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200−203. (b) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 1677−1693. (c) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 1694−1702. (d) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002−18003. (e) Hashmi, A. S. K.; Rudolph, M.; Weyrauch, J. P.; Wölfle, M.; Frey, W.; Bats, J. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 2798−2801. (f) Kennedy-Smith, J. J.; Staben, S. T.; Toste, D. F. *J. Am. Chem. Soc.* **2004**, *126*, 4526−4527.

(9) For very recent references, see: (a) Kusama, H.; Miyashita, Y.; Takaya, J.; Iwassawa, N. *Org. Lett.* **2006**, *8*, 289−292. (b) Alfonsi, M.; Arcadi, A.; Aschi, M.; Bianchi, G.; Marinelli, F. *J. Org. Chem.* **2005**, *70*, 2265−2273. (c) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349−3352.

(10) For very recent references, see: (a) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112−3113. (b) Antoniotti, S.; Genin, E.; Michelet, V.; Genet, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976−9977. (c) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962−6963. (d) Kim, N.; Kim, Y.; Park, W.; Sung, D.; Gupta, A. K.; Oh, C. H. *Org. Lett.* **2005**, *7*, 5289−5291. (e) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391−4394.

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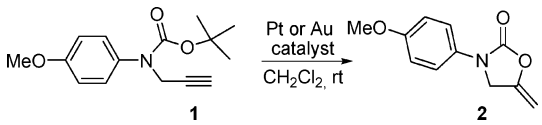
TABLE 1. Screening of Reaction Conditions for the Cyclization of Carbamate 1



1 2

entry	catalyst	time	conv.[a] (%)
1	10 mol % $Pt(CH_3CN)_2(SbF_6)_2$	24 h	80
2	10 mol % $AuCl_3$	24 h	81
3	10 mol % $Au(PPh_3)Cl$	24 h	<2
4	10 mol % $Au(PPh_3)SbF_6$	5 min	>98
5	5 mol % $Au(PPh_3)SbF_6$	5 min	>98
6	1 mol % $Au(PPh_3)SbF_6$	1 h	94

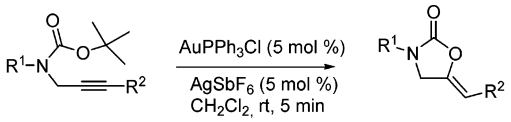
[a] Determined (%) by ^{1}H NMR in the crude mixtures.

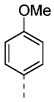
to find that treatment of **1** with 10 mol % of $Pt(CH_3CN)_2Cl_2$ (CH_2Cl_2, rt) afforded the desired oxazolidinone **2**, as a result of a 5-exo cyclization process, but the reaction did not progress to completion within 24 h (entry 1, Table 1). A similar result was obtained when 10% of gold trichloride was used (entry 2). Interestingly, whereas triphenylphosphine gold chloride was completely unreactive (entry 3), the highly electrophilic species $Au(PPh_3)SbF_6$,[13] formed by mixing equal equivalents of $Au(PPh_3)Cl$ and $AgSbF_6$,[14] proved to be more reactive, providing a complete conversion in less than 5 min (entry 4). This high catalytic activity allowed us to decrease the catalytic loading to 5 mol % without significant erosion of the observed reactivity (entry 5) or to 1 mol % (entry 6). In the last case, 94% conversion was observed after 60 min of reaction time.

With these optimized reaction conditions in hand, we next explored the scope of the process by studying a wide variety of substrates (Table 2). Alkyne-substituted BOC derivatives **3**, **5**, and **7** reacted similarly to the parent substrate **1**, providing the corresponding oxazolidinones **4**, **6**, and **8** in very short reaction times (less than 5 min with 5 mol % of catalyst) and with complete (*Z*)-stereoselectivity[15] regardless of the electronic character of the alkyne substitution (entries 2−4). Interestingly, *N*-unsubstituted oxazolidinones can be prepared in excellent yield by the cyclization of the BOC derivative of primary propargylamines (entry 5).

Good to excellent yields were also obtained from a variety of *N*-alkyl substrates (entries 6−9). Among these cases, it is noteworthy that the cyclization of the Boc derivative of the allylpropargylamine afforded exclusively the cyclic carbamate **14** without any enyne cycloisomerization product being detected[8a] (entry 7). *N*-Ferrocenyl carbamates can also be prepared in good yields using the same experimental protocol (entry 10). In contrast, no evolution at all was observed in the reaction of the

TABLE 2. Au(I)-Catalyzed Cyclization of *N*-Boc Propargylamines



ent.	subs.	R^1	R^2	prod.	yield[a]
1	**1**		H	**2**	80
2	**3**		Me	**4**	75
3	**5**		Ph	**6**	74
4	**7**		CO_2Et	**8**	95
5	**9**	H	H	**10**	92
6	**11**	Bn	H	**12**	95 (93)[b]
7	**13**	allyl	H	**14**	80
8	**15**	Et	H	**16**	69
9	**17**		H	**18**	87 (84)[b]
10	**19**		H	**20**	80
11	**21**		H	**22**	0
12	**23**	$TBSO(CH_2)_2CH_2$	H	**24**	90
13[c]	**25**	$HOCH_2CH_2$	H	**26**	88
14[c]	**27**	$HO(CH_2)_2CH_2$	H	**28**	85

[a] Yields (%) after chromatographic purification. [b] With the addition of 1 mol % catalyst, 2.5 h. [c] MeOH (10 equiv) was added.

N-pyridyl substrate **21**, likely as a result of the competitive coordination of the electrophilic gold atom to the basic pyridyl nitrogen (entry 11). Although all these cyclizations were carried out with 5 mol % of gold catalyst, in the case of substrates **11** and **17**, we confirmed that the process can be performed with 1 mol % of catalyst with small erosion of the chemical yield (values in brackets in entries 6 and 9), although the reaction times were much longer (a few hours instead of 5 min). Interestingly, from a practical point of view, it was also proved from substrate **11** that the cyclization with 1 mol % of catalyst can be run at a higher substrate scale (20 mmol instead of the 0.3−0.5 mmol scale routinely employed) giving the product **12** in 85% yield (Supporting Information).

This procedure also tolerates the presence of functional groups at the nitrogen chain, such as silyl ethers (entry 12) or alcohols

(11) During the preparation of this manuscript, the Au(I)-catalyzed cyclization of alkynyl *tert*-butyl carbonates has been reported: (a) Buzas, A.; Gagosz, F. *Org. Lett*. **2006**, 3, 515−518. (b) Kang, J.-E.; Shin, S. *Synlett* **2006**, 717.

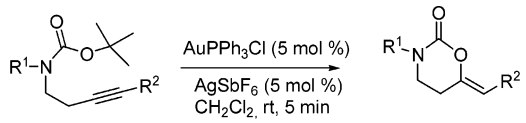
(12) Substrate **1** was prepared in 91% yield by the reaction of *N*-Boc-*p*-anisidine with propargyl bromide. See Supporting Information for details.

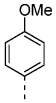
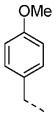
(13) For recent examples of the utilization of cationic gold complex generated from $AuPPh_3Cl$ and silver salts, see for instance: ref 8b,c,e,f. See also: Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc*. **2006**, *128*, 1798−1799.

(14) In the absence of $AuPPh_3Cl$, the use of $AgSbF_6$ alone as catalyst provided the cyclization product **2** but with only 73% of conversion after 24 h.

(15) The stereochemistry was assigned in the case of oxazolidinone **6** by a NOESY experiment (a strong cross-peak was observed between the olefinic proton and the allylic protons).

TABLE 3. Cationic Au(I)-Catalyzed Reaction of *N*-Boc-3-butyn-1-amines



entry	subs.	R^1	R^2	product	yield[a]
1	**29**	Bn	H	**30**	90
2	**31**	Bn	CO_2Et	**32**	91
3	**33**		H	**34**	81
4	**35**		H	**36**	75

[a] Yields (%) in pure isolated products.

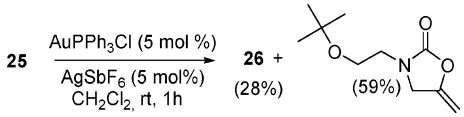
(entries 13 and 14). Although, in the later case, it could be envisaged the participation of the hydroxyl group as an internal competitive nucleophile in the addition to the gold-activated alkyne,[16] only oxazolidinone products were formed. Nevertheless, under the standard reaction conditions, the oxazolidinone having a pendant *tert*-butoxy group was formed as the major product, likely as a result of the final *tert*-butylation of the hydroxyl group with the isobutene presumably produced in the reaction.[17] To avoid this side reaction, the cyclization was run in the presence of 10 equiv of MeOH as the trapping agent. In this way, the corresponding hydroxyl-substituted oxazolidinones **26** and **28** were obtained in high yields (85 and 88% yields, respectively).

Having established that *N*-Boc propargylamines are suitable substrates for Au(I)-catalyzed cyclization, we next examined the reaction of the homologous *N*-Boc-3-butyn-1-amines,[18] which would lead to the six-membered 2-oxazinones through a 6-exo cyclization pathway. As it is deduced from the four cases collected in Table 3, the reaction is as fast and efficient as in the case of the propargylamine substrates. The corresponding cyclic carbamates were obtained in good yields (75−91%) regardless of the substitution at nitrogen and alkyne terminus (entries 1−4).

A tentative mechanism for this gold-catalyzed cyclization involves the nucleophilic attack of the carbamate carbonyl group

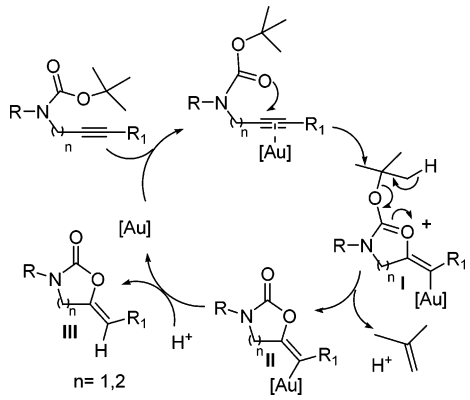
(16) For gold-catalyzed addition of alcohols to alkynes, see ref 10b,c.

(17) For instance, in the absence of added MeOH, the cyclization of **25** with $AuPPh_3Cl/AgSbF_6$ (5 mol %) in CH_2Cl_2 (2 h) afforded a 35:65 mixture of the oxazolidinone **26** and its *tert*-butyl ether. These compounds were isolated in 28 and 59% yields after silica gel chromatography.



(18) These substrates were prepared by a reaction of 3-butynyl-1-methanesulfonate with the corresponding amine and further BOC protection. See: Fürstner, A.; Guth, O.; Düffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem.*−*Eur. J.* **2001**, *7*, 4811−4820.

SCHEME 1. Proposed Mechanism for the Formation of Alkylidene Cyclic Carbamates



on the activated Au(I)−alkyne complex to afford the cationic vinyl−gold intermediate **I**. Subsequent *tert*-butyl fragmentation,[19] likely by releasing isobutene and a proton, would give rise the oxazolidinone−Au complex **II**, which after protonation would provide the observed oxazolidinone **III** (Scheme 1).[20] In concordance with this mechanistic hypothesis, no reaction at all was observed, even after 24 h, in the attempts of gold-promoted cyclization of the *N*-methyl carbamate of propargylamines instead of its BOC derivative.

In conclusion, the Au(I)-catalyzed cyclization of the BOC derivative of propargylamines and 3-butynamines provides a general and efficient access to alkylidene 2-oxazolidinones and 1,3-oxazin-2-ones under very mild neutral reaction conditions. This procedure is highly tolerant with regard to the substitution at nitrogen and alkyne moiety.

Experimental Section

Typical Procedure for the Au(I)-Catalyzed Synthesis of Oxazolidinones. *N*-(4-Methoxyphenyl)-5-methylidene-2-oxazolidinone (2): A round-bottomed flask was charged with $AuClPPh_3$ (7.6 mg, 0.015 mmol) and $AgSbF_6$ (5.3 mg, 0.015 mmol), capped with a rubber septum, evacuated, and backfilled with nitrogen. Anhydrous CH_2Cl_2 (3 mL) was added, and the resulting reaction mixture was stirred at room temperature for 1 h. A solution of **1** (80 mg, 0.30 mmol) in CH_2Cl_2 (3 mL) was added via syringe to the catalyst solution, and the reaction mixture was stirred at room temperature for 5 min. The crude reaction mixture was filtered through a plug of Celite with the aid of CH_2Cl_2, and the solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (hexane/AcOEt, 10/1) to afford the oxazolidinone **2** (48.3 mg, 77%, white solid). Mp 138−139 °C. ^{1}H NMR (200 MHz, $CDCl_3$): 7.44 (d, J = 9.3 Hz, 2H), 6.91 (d, J = 9.3 Hz, 2H), 4.84 (q, J = 3.0 Hz, 1H), 4.61 (t, J = 2.5 Hz, 2H), 4.40 (q, J = 3.0 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 156.7, 152.6, 147.9, 130.3, 120.2, 114.4, 86.9, 55.5, 48.9. MS (ESI+): 206 (MH^+, 100%), 228 (MNa^+, 58%). HRMS (ESI+) calcd for $(C_{11}H_{12}NO_3)[MH^+]$, 206.0810; found, 208.0811 and for $(C_{11}H_{11}NO_3Na)[MNa^+]$, 228.0631; found, 228.0631.

(19) For other processes with the *N*-Boc group acting as nucleophile in cyclization reactions, see for instance: (a) Hanessian, S.; Tremblay, M.; Marzi, M.; Del Valle, J. R. *J. Org. Chem.* **2005**, *70*, 5070−5085. (b) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1990**, *55*, 1447−1459.

(20) It has also been confirmed that the cyclization requires the activation of the alkyne moiety by the gold catalyst and that it is not simply an acid-catalyzed process. Thus, after treating **1** with TFA or TsOH in CH_2Cl_2 at room temperature, cyclic products were not detected at all and only partial or complete *N*-Boc deprotection was observed.

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Supporting Information Available: Experimental procedures for the preparation of the starting alkynyl carbamates. Copies of ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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