JOC Note

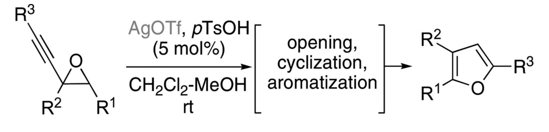
Silver(I)-Catalyzed Cascade: Direct Access to Furans from Alkynyloxiranes

Aurélien Blanc, Katharina Tenbrink, Jean-Marc Weibel, and Patrick Pale*

Laboratoire de Synthèse et Réactivité Organiques, associé au CNRS, Université de Strasbourg, Institut de Chimie, 4 rue Blaise Pascal, 67000 Strasbourg, France

ppale@chimie.u-strasbg.fr

Received March 4, 2009

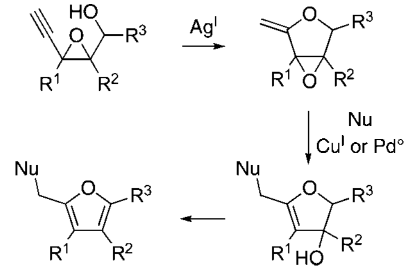


Functionalized furans are conveniently formed by a new silver(I)-catalyzed reaction of alk-1-ynyl oxiranes in the presence of *p*-toluenesulfonic acid and methanol. Evidence supported a cascade mechanism.

Furans are important compounds in organic chemistry as such motifs occur in many natural products, as well as in various pharmaceutical products and flavor and fragrance compounds. Furans also act as key building blocks in the synthesis of numerous substances.[1] Due to such wide interest, several furan syntheses have already been developed,[1,2] but any new synthetic method able to provide highly substituted furans under mild conditions would be particularly valuable.

Among the developed methods, the cyclization or rearrangement of allene or alkyne derivatives catalyzed by late transition metals is particularly interesting due to convergence. Mercury was originally proposed for such cyclization,[3] but toxicity and compatibility with functional groups led to the use of palladium as catalyst.[4] Platinum was more recently explored as catalyst for such reactions,[5,6] but gold exhibited higher flexibility due to its mildness.[7,8] Surprisingly, silver salts, inexpensive compared to gold or platinum salts, were almost never applied to a one-step formation of furans and only two methods, both reported by Marshall, have been described.[9] The first one was based on the cyclization of allenones using a catalytic amount of silver nitrate in acetone.[10] The second one used the combination of silver nitrate and silica gel to cyclize β-methylene alkynols affording furans in high yields.[11] Very recently, these conditions were applied to the synthesis of furans from 3-alkyne-1,2-diols[12] or *gem*-difluorohomopropargyl alcohols[13] in a cyclization—elimination process. Some years ago, our group[14] reported a two-step approach to furans based on the cyclization of epoxyalkynols and nucleophilic addition (Scheme 1), and taking advantage of the mild Lewid acid properties of silver ion, we wondered if a one-pot procedure could be amenable. In the presence of Ag^I, a nucleophile would open the epoxide either in a S_N2 process or in a S_N2' process, leading to an allenol or an alkynol. Both cyclized in the presence of Ag^I and produced dihydrofurans (Scheme 2).

SCHEME 1. Two-Step Ag-Promoted Synthesis of Furans and Dihydrofurans from Epoxyalkynols[14]



Although known with copper,[15] palladium,[4a] and gold,[8d−f,16] nucleophilic additions to alkynyloxiranes appeared to be unprecedented with silver.[9] This lack of results incited us to examine the reactivity of readily available α-alkynyl epoxides[17]

---

(1) (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795–819. (b) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955–2020. (c) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491–2515.

(2) (a) Eicher, T.; Hauptmann S. *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH: Weinheim, 2003. (b) Bird, C. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven E. F. V., Eds.; Elsevier Science Ltd.; Oxford, 1996; Vol. 2.

(3) Miller, D. *J. Chem. Soc. C* **1969**, 12–15.

(4) (a) Minami, I.; Yuhara, M.; Watanabe, H.; Tsuji, J. *J. Organomet. Chem.* **1987**, *334*, 225–242. (b) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5816–5819. (c) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **1995**, *34*, 1581–1583. (d) Seiller, B.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1995**, *51*, 13089–13102. (e) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280–9288. (f) Ma, S. M.; Zhang, J. L.; Lu, L. H. *Chem.—Eur. J.* **2003**, *9*, 2447–2456.

(5) Yoshida, M.; Al-Amin, M.; Matsuda, K. S. *Tetrahedron Lett.* **2008**, *49*, 5021–5023.

(6) (a) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022–15023. (b) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024–15025. (c) Fürstner, A.; Heilmann, E. K.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 4760–4763.

(7) Hashmi, A. S. K.; Pradipta, S. *Adv. Synth. Catal.* **2004**, *346*, 432–438.

(8) (a) Hashmi, A. S. K.; Schwarz, L.; Choi, J. H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285–2288. (b) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164–11165. (c) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679–7685. (d) Shu, X.-Z.; Liu, X.-Y.; Xiao, H.-Q.; Ji, K.-G.; Guo, L.-N.; Qi, C.-Z.; Liang, Y.-M. *Adv. Synth. Catal.* **2007**, *349*, 2493–2498. (e) Ji, K.-G.; Shen, Y.-M.; Shu, X.-Z.; Xiao, H.-Q.; Bian, Y.-J.; Liang, Y.-M. *Adv. Synth. Catal.* **2008**, *350*, 1275–1280. (f) Dai, L.-Z.; Shi, M. *Tetrahedron Lett.* **2008**, *49*, 6437–6439.

(9) For recent reviews on silver chemistry, see: (a) Weibel, J.-M.; Blanc, A. P.; Pale, *Chem. Rev.* **2008**, *108*, 3149–3173. (b) Alvarez-Corral, M.; Munoz-Dorado, M.; Rodriguez-Garcia, I. *Chem. Rev.* **2008**, *108*, 3174–3198. (c) Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3199–3222. (d) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442. (e) Halbes-Letinois, U.; Weibel, J.-M.; Pale, P. *Chem. Soc. Rev.* **2007**, *36*, 759–769.

(10) Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450–3451.

(11) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966–5968.

(12) Hayes, S. J.; Knight, D. W.; Menzies, M. D.; O'Halloran, M.; Tan, W.-F. *Tetrahedron Lett.* **2007**, *48*, 7709–7712.

(13) Arimitsu, S.; Hammond, G. B. *J. Org. Chem.* **2007**, *72*, 8559–8567.

(14) (a) Chuche, J.; Pale, P. *Tetrahedron Lett.* **1987**, *28*, 6447–6448. (b) Dalla, V.; Pale, P. *Tetrahedron Lett.* **1996**, *37*, 2781–2784. (c) Chuche, J.; Pale, P. *Eur. J. Org. Chem.* **2000**, 1019–1025.

(15) (a) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1989**, *30*, 2387–2390. (b) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron* **1991**, *47*, 1677–1686.

10.1021/jo900483m CCC: $40.75 © 2009 American Chemical Society
Published on Web 04/28/2009

SCHEME 2. Proposed Ag-Catalyzed Transformations of Alkynyloxiranes to Dihydrofurans and/or Furans

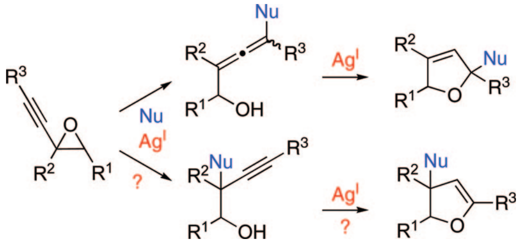
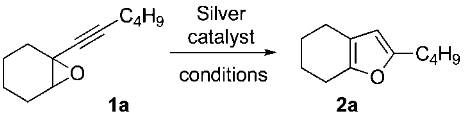


TABLE 1. Screening of Reaction Conditions for the Transformation of the Alkynyl Oxirane 1a



1a **2a**

entry	catalyst (mol %)	conditions[a]	time (h)	yield[b] (%)
1	AgCl (5)	CH_2Cl_2 (dry), rt	24	0
2	$AgNO_3$ (5)	CH_2Cl_2 (dry), rt	24	0
3	$AgNO_3$ (5)	MeOH, rt	24	40[d]
4	AgOTf (5)	CH_2Cl_2 (dry),rt	24	20[c]
5	AgOTf (5)	CH_2Cl_2/MeOH (9/1), rt	24	73
6	AgOTf (5)	MeOH, rt	24	72
7	$AgSbF_6$ (5)	CH_2Cl_2/MeOH (9/1), rt	24	55[d]
8	$AgNTf_2$ (5)	CH_2Cl_2/MeOH (9/1), rt	24	41[d]
9	AgOTf/*p*-TsOH (5/5)	CH_2Cl_2/MeOH (9/1), rt	24	**80**
10	AgOTf/*p*-TsOH (5/5)	CH_2Cl_2/MeOH (9/1), −78 °C	24	55
11	AgOTf/*p*-TsOH (5/5)	CH_2Cl_2/MeOH (9/1), 40 °C	24	Traces[d]
12	*p*-TsOH (5)	CH_2Cl_2 (dry), rt	24	0
13	*p*-TsOH (5)	MeOH, rt	0.5	0[e]
14	AgOTf/*p*-TsOH (5/5)	CH_2Cl_2/EtOH (9/1), rt	24	23
15	AgOTf/TsOH (5/5)	CH_2Cl_2/*t*-BuOH (9/1), rt	24	35

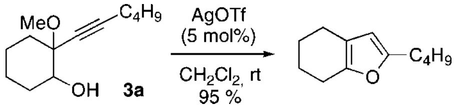
[a] Reactions run under argon, $c = 0.1$ mol/L. [b] Yields of **2a** were calculated from ^{1}H NMR spectra relative to an internal standard (hexamethylbenzene). [c] Depending on AgOTf source, variations in yield were noticed, see ref 19. [d] Degradation occurred leading to unidentified byproduct. [e] Product resulting from epoxide opening (see Scheme 3) was obtained.

in the presence of silver salts. We report here that highly substituted furans were easily obtained by silver-catalyzed transformation of alkynyloxiranes in the presence of alcohols.

In order to find more appropriate conditions for the reaction, we applied various conditions and silver catalysts to the readily available 1-(hex-1-ynyl)-1,2-epoxycyclohexane[18] **1a** in the presence or absence of alcohol (Table 1).

Silver chloride alone did not promote any transformation, and the starting material **1a** was recovered even after prolonged contact time (entry 1). The same observations were gained with silver nitrate (entry 2). However, in pure methanol, a new compound **2a** was produced in reasonable yield (entry 3). Spectroscopic data of this new compound revealed the disappearance of the epoxide and acetylenic units and the presence of an aromatic moiety, suggesting a tetrahydrobenzofuran structure for **2a**. As expected, methanol acted as nucleophile in this reaction, but it seemed that the expected dihydrofuran was not stable under these conditions and aromatization occurred leading to the observed furan (cf. Schemes 2 and 3).

SCHEME 3. Ag-Promoted Formation of Furan from *β*-Methoxy-*β*-alkynol



The more electrophilic and soluble silver triflate alone surprisingly proved effective enough in dichloromethane to cleanly convert **1a** into the furan **2a**, although in modest and variable yields (entry 4).[19] As expected, the addition of methanol as nucleophile dramatically increased the conversion, and **2a** was isolated in good yield (entry 5). Running the reaction in pure methanol did not improve yield (entry 6).

Switching to the even more electrophilic silver hexafluoroantimonate and triflimido salt led to complete conversion in dichloromethane in the presence of methanol, providing the same compound **2a** but in moderate yields due to some degradation (entries 7 and 8).

In order to improve the efficiency of the reaction, we screened several cocatalysts, which could facilitate the oxirane opening without altering the silver catalyzed cyclization. We eventually found that *p*-toluenesulfonic acid was the best compromise. In the presence of 5 mol % of this acid and 5 mol % of silver triflate, **1a** was efficiently converted to the furan **2a** in a mixture of dichloromethane and methanol (entry 9). Control experiments with *p*-toluenesulfonic acid alone revealed that almost no reaction occurred without silver salt or methanol (entry 12). However, and as expected, *p*-toluenesulfonic acid alone in pure methanol or in mixtures of dichloromethane and methanol led to the epoxide opening product (entry 13; see below). Under the best conditions (entry 9), increasing or lowering the temperature did not further improve the reaction and proved even deleterious, the yield of furan being lowered (entries 10 and 11).

Other hydroxy nucleophiles did not give satisfactory results under the same conditions. A rapid screening confirmed that bulkier alcohols are less efficient (entries 14 and 15).[20]

With these conditions in hand, we briefly investigated the scope of this new formation of furans. Various representative alkynyl oxiranes **1b**−**k**, easily prepared by *m*-CPBA epoxidation of the corresponding enynes, were then submitted to the above conditions (Table 2).

The six-membered hexynyl epoxide **1a** was used as reference for comparison purposes (entry 1), and the ring size as well as the alkyne side chain were varied. With the strained five-membered derivative **1b**, we expected an easier reaction. However, degradation mostly occurred, and the expected product could be barely detected (entry 2). The seven-membered derivative **1c** behaved as the six-membered **1a**, but the furan formation was slightly less effective (entry 3 vs 1). With the eight-membered derivative **1d**, the expected furan **2d** was isolated in excellent yield (entry 4 vs 1).

---

(16) (a) Dai, L.-Z.; Qi, M.-J.; Shi, Y.-L.; Liu, X.-G.; Shi, M. *Org. Lett.* **2007**, *9*, 3191–3194. (b) Shu, X.-Z.; Liu, X.-Y.; Ji, K.-G.; Xiao, H.-Q.; Liang, Y.-M. *Chem.—Eur. J.* **2008**, *14*, 5282–5289. (c) Hashmi, A. S. K.; Bührle, M.; Salathé, R.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 2059–2064. (d) Lin, G.-Y.; Li, C.-W.; Hung, S.-H.; Liu, R.-S. *Org. Lett.* **2008**, *10*, 5059–5062. (e) Dai, L.-Z.; Shi, M. *Chem.—Eur. J.* **2008**, *14*, 7011–7018.

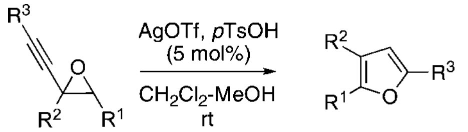
(17) For a review of alkynyloxirane preparations, see: Chemla, F.; Ferreira, F. *Curr. Org. Chem.* **2002**, *6*, 539–570.

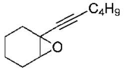
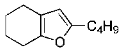
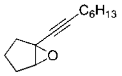
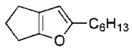
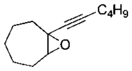
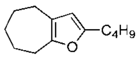
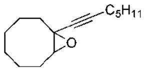
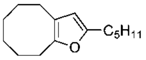
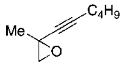
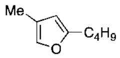
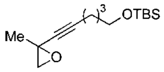
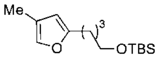
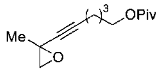
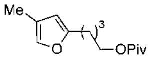
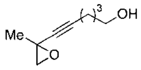
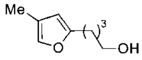
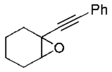
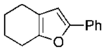
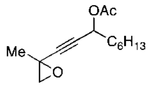
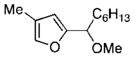
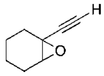
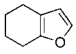
(18) Compound **1a** was obtained following Carlson's procedure: Carlson, R. G.; Cox, W. W. *J. Org. Chem.* **1977**, *42*, 2382–2386.

(19) Traces of water or alcohols contained in the solvent or the reagents were probably responsible for catalysis of this reaction (see Scheme 4), and carefully dried solvent and reagents have to be used to miminize it.

(20) Nucleophiles based on other heteroatoms probably poisoned the catalyst, while carbon nucleophiles are currently explored.

TABLE 2. **Scope of the Ag- and Acid-Catalyzed Rearrangement of Alkynyloxiranes to Furans**



entry	alkynyloxiranes		time (h)	furans		yield (%)[a]
1		**1a**	24		**2a**	80
2		**1b**	24		**2b**	-[b]
3		**1c**	3		**2c**	72
4		**1d**	3		**2d**	92
5		**1e**	16		**2e**	76
6		**1f**	16		**2f**	84
7		**1g**	16		**2g**	81
8		**1h**	2		**2h**	52
9		**1i**	24		**2i**	11[b]
10		**1j**	16		**2j**	56
11		**1k**	72		**2k**	-[b]

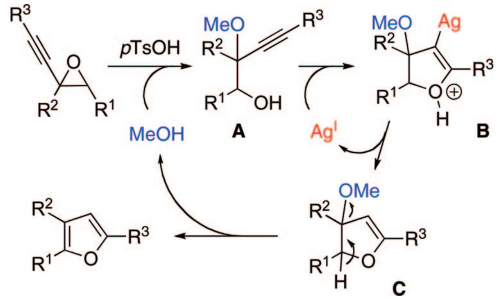
[a] Isolated yields. [b] Degradation occurred leading to unidentified byproduct.

When not embedded in a cycle, alkynyloxiranes behave in the same way, giving the corresponding furans in good yields, similar to those achieved with the six-membered epoxide **1a** (entries 5−7 vs 1). It is interesting to note that the functionalized side chain did not interfere in the reaction. Interestingly, the corresponding nonprotected epoxyalkynol **1h** did give the expected furan **2h**, despite obvious competition with the added nucleophile (methanol) present in the reaction mixture (entry 8). Protection as ester or silyl ether proved nevertheless beneficial, the corresponding furans being isolated in higher yields (entries 6 and 7 vs 8).

Epoxyalkynes in which the alkyne was conjugated with unsaturated group did not react well under these conditions. For example, the phenylethynyl epoxide **1i** led to a mixture of products from which the expected furan **2i** could only be isolated in low yield (entry 9).

Interestingly, (3-acetyloxyprop-1-ynyl)oxirane derivative, which has been described to rearrange to divinyl ketones in the presence on Ag or Au salts,[21] afford the furan **2j** in modest yield but with incorporation of methanol in place of acetyl group (entry 10).

SCHEME 4. **Proposed Mechanism for the Ag- and Acid-Catalyzed Rearrangement of Alkynyloxiranes to Furans**



Finally, the simplest ethynyl derivate **1k** only led to decomposition, probably due to the formation of alkynylsilver under these conditions (entry 11).

As the present Ag- and acid-catalyzed rearrangement of alkynyloxiranes to furans probably involved the intermediate opening of the starting alkynyloxiranes (cf. Scheme 2), we prepared such products and checked whether they indeed can be cyclized into furans by catalytic amounts of silver triflate.

The 1,2-epoxyhex-1-ynylcyclohexane **1a** was again used as substrate. The corresponding opening product **3a** was easily obtained in high yield upon treatment by methanol in the presence of acids, including *para*-toluenesulfonic acid. As expected, *p*-TsOH was not able to promote cyclization (see Table 1, entry 12), whereas catalytic amounts of silver triflate in dichloromethane smoothly converted **3a** to the corresponding furan **2a** (Scheme 3).

These results thus validated our proposed pathway involving a cascade of events (Scheme 4), in contrast to the direct cyclization usually proposed for Au- and Pt-catalyzed furan formations.[5,7] The starting alkynyloxirane probably is first opened by an alcohol in a nucleophilic substitution promoted by the catalytic amounts of *p*-toluenesulfonic acid. It is worth noting that electrophilic silver salts can nevertheless promote this reaction opening (see Table 1, entries 3 and 5−7). The so formed β-alkoxy-β-alkynol **A** would then cyclize upon coordination with silver ion, leading to heterocyclic vinyl silver species **B**. Protodemetalation then regenerates the catalyst and gives 4-alkoxy-4,5-dihydrofuran **C**. Upon elimination of alcohol, the latter would be converted to a furan derivative. This elimination could be facilitated either by the acid present or by the mild Lewis acid silver ion.

In conclusion, we have reported *for the first time* a one-step catalytic approach to functionalized furans through an Ag-catalyzed cascade reaction of α-alkynyl oxiranes. The reaction proceeds efficiently under mild conditions. Further work is now underway in our laboratory to broaden the scope of this reaction and to better understand its mechanism.

Experimental Section

General Procedure for Silver(I)-Catalyzed Formation of Furans from Alkynyloxiranes. To a solution of alkynyloxirane (1 mmol) in CH_2Cl_2/MeOH (5 mL, 9/1 v/v) were added successively *p*-toluenesulfonic acid (*p*-TsOH, 0.05 mmol) and AgOTf (0.05 mmol) at room temperature. The reaction was monitored by thin-layer chromatography until completion. The reaction mixture was filtered throughout a pad of silica gel with CH_2Cl_2. Solvents were removed in vacuo, and the crude residue was purified by flash chromatography (cyclohexane/EtOAc).

---

[21] Cordonnier, M.-C.; Blanc, A.; Pale, P. *Org. Lett.* **2008**, *10*, 1569–1572.

2-Butyl-4,5,6,7-tetrahydrobenzofuran (2a). Following the general procedure, alkynyloxirane **1a** (100 mg, 0.56 mmol) gave **2a** (80 mg, 80%) as a colorless oil: $R_f = 0.64$ (cyclohexane/EtOAc 20%); IR (neat) ν_{max} 2935, 2870, 1738, 1674, 1520, 1446, 1379, 1220, 1165, 1120, 1095, 982 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.94 (t, $J = 7.3$ Hz, 3 H), 1.39 (sext, 7.4 Hz, 2 H), 1.58 (quint, $J = 5.7$ Hz, 2 H), 1.66−1.75 (m, 2 H), 1.78−1.85 (m, 2 H), 2.37−2.40 (m, 2 H), 2.54−2.60 (m, 4 H), 5.79 (s, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 13.8, 22.1, 22.3, 23.1, 23.2, 23.3, 27.8, 30.4, 105.4, 117.1, 148.6, 154.2; MS (ESI) m/z 357 (100, $2M^{+\bullet} + 2H$), 179 (95, $M^{+\bullet} + H$); HR-MS 179.1438 ($C_{12}H_{18}O + H$ calcd 179.1430).

Acknowledgment. We thank the CNRS and the French Ministry of Research for financial support. K.T. thanks the Friedrich-Alexander-Universität Erlagen-Nürnberg and ULP for their exchange program and support.

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

JO900483M