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A Silver-Catalyzed Spirocyclization of Alkynyl Silyl Enol Ethers

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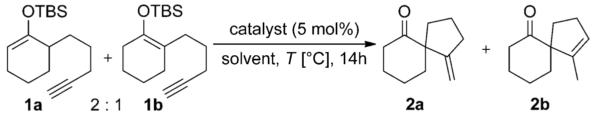
Spiro compounds are of great interest because of their special conformational features and their structural implications on biological systems.[1] The presence of the sterically constrained spiro structure in various natural products substantially promotes interest in the investigation of spiro compounds.[2] The Conia-ene cyclization is one of the processes during which a quaternary center is formed by the pericyclic reaction of an enolizable carbonyl group with an alkyne. However, the need for high temperatures limits the synthetic utility of this reaction.[3] On the other hand, transition-metal-catalyzed versions[4] proceed under mild conditions at lower temperatures. Toste and co-workers have reported a phosphine–gold(I)-catalyzed version for the intramolecular addition of a β-ketoester to an unactivated alkyne.[5] In a similar reaction, Davies and Detty-Mambo demonstrated the cycloisomerization of unactivated ketones with alkynes under gold catalysis.[6] In recent years, silver salts have gained increasing interest in homogeneous catalysis owing to their mildness and efficiency.[7] More recent reviews discuss the current revolution in silver chemistry. Catalysis with silver salts has become widespread due to the σ and π Lewis acidic properties of silver(I) complexes,[8] which lead to a variety of chemical transformations.[9] Therefore, exploring new catalytic reactions with silver complexes is of great interest. For this reason, we focused on silver-catalyzed cycloisomerization to study the behavior of alkynyl silyl enol ethers.

Mainly used as cocatalysts in gold catalysis, silver salts, such as $AgBF_4$, $AgSbF_6$, and $AgPF_6$, are very hygroscopic, causing difficulties in properly weighing the reagent and keeping the reaction medium nonacidic. In contrast, $AgNTf_2$ (Tf = triflyl)[10] is known to be more stable and easier to handle than its congeners. Thus, this reagent proved to be an efficient catalyst for nucleophilic additions to alkynes.[11] For this purpose, we envisaged the use of $AgNTf_2$ as a potentially valuable candidate for the cycloisomerization of silyl alkynyl enol ethers.

We began our investigation by examining the cyclization using various silver catalysts with different solvents for the reaction of compound **1** (Table 1). Interestingly, the use of $AgNTf_2$ alone led to spiro compounds **2a** and **2b** with the same yield as that observed under gold catalysis (Table 1, entry 3). Furthermore, the yield could be improved by using CH_2Cl_2 or toluene as the solvent (Table 1, entries 4 and 7). Control experiments revealed that silver carbonate or the corresponding free amine, that is, triflimide, could not catalyze the reaction of silyl alkynyl enol ethers to form spiro compounds, and no reaction occurred under metal-free conditions. Likewise, the unsilylated ketones could not be transformed into the spiro compounds.

Table 1. Screening of solvents and catalysts (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene).



Entry	Catalyst	Solvent	T [°C]	Yield [%][b]	**2a/2b**
1	IPrAuCl/AgOTf	$ClCH_2CH_2Cl$	84	12 (63)	100:0
2	IPrAuCl/$AgNTf_2$	$ClCH_2CH_2Cl$	84	66	2.5:1
3	$AgNTf_2$	$ClCH_2CH_2Cl$	20	67	17:1
4	$AgNTf_2$	CH_2Cl_2	20	78	16:1
5	$AgNTf_2$	THF	20	41 (40)	20:1
6	$AgNTf_2$	acetone	20	–[c]	–
7	$AgNTf_2$	toluene	20	76	9:1
8	$AgNTf_2$	CH_3CN	82	7 (65)	1:5
9	$AgNTf_2$	$ClCH_2CH_2Cl$/MeOH	20	–[c]	–
10	$AgNTf_2$	toluene[a]	20	56 (12)	1:38
11	$AgNTf_2$	$ClCH_2CH_2Cl$	20	–[c]	–
12	Ag_2CO_3	$ClCH_2CH_2Cl$	20	–[c]	–
13	–	$ClCH_2CH_2Cl$	20	–[d]	–

[a] Toluene was not distilled before use. [b] Yields in parentheses correspond to the deprotected starting material. [c] Only deprotection of the starting material occurred. [d] The starting material was recovered.

Having found that Ag^I-catalyzed cycloisomerization favors the 5-*exo*-dig cyclization process, we evaluated the scope of the reaction by using various alkynyl cycloalkanones. The reaction proved to be quite general, although the yield is dependent upon both the substrate and the solvent (Table 2, entries 1, 2, 13–16, and 19). Interestingly, in most cases that use CH_2Cl_2 as the solvent, the *exo* regioisomer is favored, except for entries 6, 18, and 22 in Table 2, whereas the *endo* compound is obtained in toluene except for cyclo-

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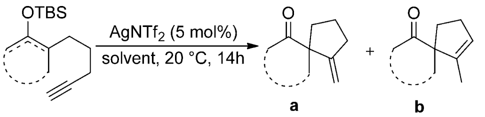
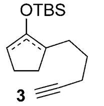
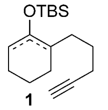
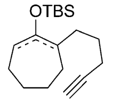
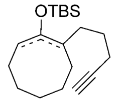
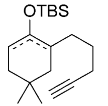
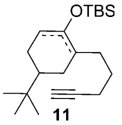
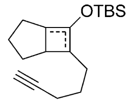
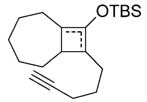
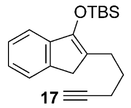
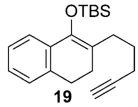
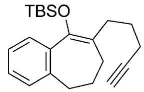
Table 2. Ag^I-catalyzed spirocyclization.

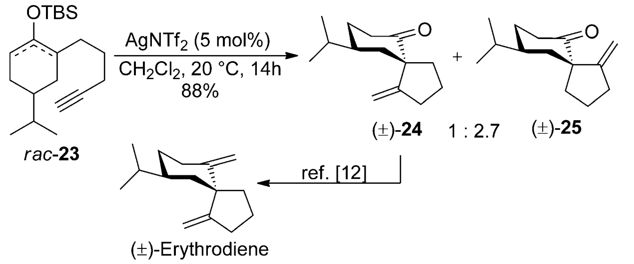


a b

Entry[a]	Substrate	Solvent	Product	Yield [%][a]	a/b
1	 **3**	toluene	**4**	47	100:0
2		CH_2Cl_2		35	5:1
3	 **1**	toluene	**2**	76	9:1
4		CH_2Cl_2		78	16:1
5	 **5**	toluene	**6**	74	1:9[b]
6		CH_2Cl_2		62	0:100
7	 **7**	toluene	**8**	48 (4)	1:2[b]
8		CH_2Cl_2		58 (9)	2:1[b]
9	 **9**	toluene	**10**	64 (12)	0:100
10		CH_2Cl_2		71 (15)	100:0
11	 **11**	toluene	**12**	72	1:25[c]
12		CH_2Cl_2		83	28[c]:1
13	 **13**	toluene	**14**	trace	1:2
14		CH_2Cl_2		trace	100:0
15	 **15**	toluene	**16**	0 (31)	–
16		CH_2Cl_2		13 (59)	100:0
17	 **17**	toluene	**18**	74	0:100
18		CH_2Cl_2		75	1:7
19	 **19**	toluene	**20**	25 (25)	1:3
20		CH_2Cl_2		59 (23)	100:0
21	 **21**	toluene	**22**	74 (10)	0:100
22		CH_2Cl_2		49 (35)	0:100

[a] Yields in parentheses correspond to the deprotected starting material. [b] The product of a 6-*endo* cyclization reaction is obtained instead of the 5-*exo* product. [c] Obtained as a mixture of diastereoisomers.

pentanone and cyclohexanone derivatives (Table 2, entries 1 and 3) for which the *exo* regioisomer is always the major product. Silyl alkynyl enol ethers derived from larger rings furnished 6-*endo*-dig cyclization products (Table 2, entries 5, 7, 8).



Scheme 1. The formal total synthesis of (±)-erythrodiene (TBS = *tert*-butyldimethylsilyl).

In this way, by starting from compound **23**, a mixture of spiroketones **24** and **25** was obtained (Scheme 1), the first of which was elaborated into spirobicyclic sesquiterpene (±)-erythrodiene by Huang and Forsyth.[12]

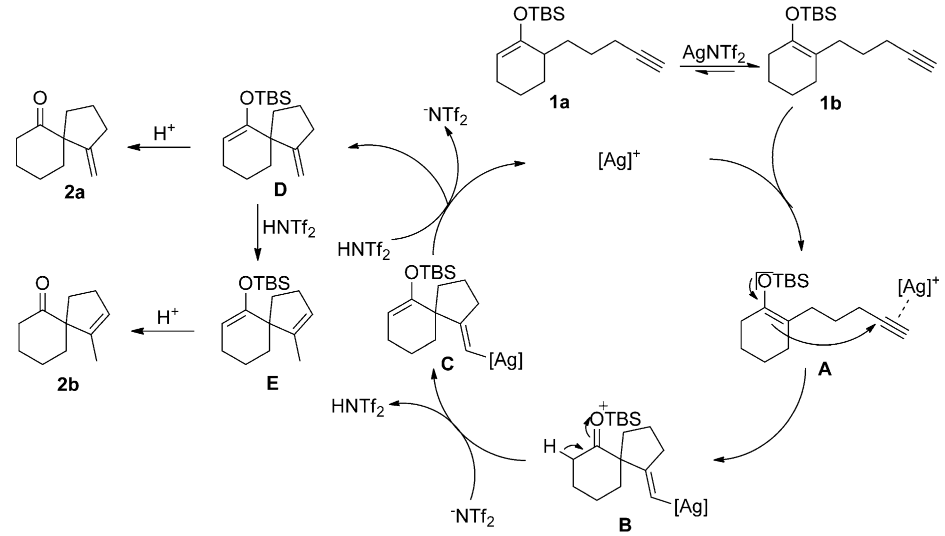
A tentative mechanism for this Ag-catalyzed cycloisomerization reaction is outlined in Scheme 2. Based on the fact that alkynyl silyl enol ethers **1a** and **1b** are present as a 2:1 mixture, it seems that under silver catalysis isomerization from **1a** to **1b** takes place.[13] Complexation of the silver salt to the alkynyl moiety would initiate this process. After the complexation step, intermediate **A** could undergo an ene–yne cycloisomerization assisted by the alkyne activation[14] and the presence of the oxygen atom to yield the intermediate silver complex **B**. Then, proton migration would give product **C**. Subsequent protonolysis of the alkenyl–silver species and hydrolysis of the silyl enol ether would afford either the 5-*exo*-dig isomer **2a**[15] or further isomerization of *exo*-silyl enol ether **D** in the presence of $HNTf_2$ would lead (via **E**) to the *endo* product **2b.** The isomerization step has been proven by the treatment of **20a** with $HNTf_2$, which gave compound **20b** in 97% yield (Scheme 3).[16]

To further highlight the potential of this new silver-catalyzed spirocyclization, we attempted to trap the newly formed alkenyl–silver intermediate prior to protonation with a source of electrophilic iodine.[17] This type of transformation would be of high synthetic interest because it would lead to alkenyl iodides.[18]

Thus, alkynyl silyl enol ethers were treated in a one-pot reaction with $AgNTf_2$ (5 mol%), directly followed by addition of *N*-iodosuccinimide (NIS) in $ClCH_2CH_2Cl$, which provided exclusively the *E*-alkenyl iodide derivatives in good yields (Table 3).[19] It should be noted that in this case no 6-*endo* compounds were isolated and the reaction of **1** with NIS alone led exclusively to the α-halogenated derivative of the desilylated starting material.[16]

Although the silver-catalyzed cycloisomerization of bicyclo[3.2.0]alkanone **13** proved to be difficult, iodo-demetalation makes it possible to obtain alkenyl iodide derivative **31**. The X-ray crystal structure of tricyclic alkenyl iodide **31** (Figure 1) showed an *E*-configured *exo* double bond, thus, providing evidence for the iodo-demetalation of intermediate **C** with the NIS reagent.[17]

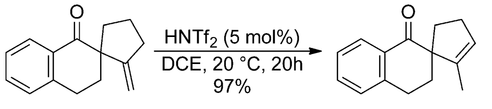
In light of this result, we considered the possibility that a similar silver-catalyzed pathway could account for activated alkynes. To our delight, subjecting alkynoate **35** to the



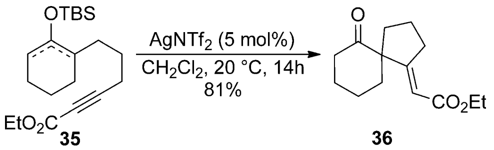
Scheme 2. Mechanistic proposal for the $AgNTf_2$-mediated cyclization reactions.

silver-catalyzed cycloisomerization conditions afforded spiroester **36** in 81 % yield (Scheme 4).

In summary, a silver(I)-catalyzed intramolecular addition reaction of silyl enol ethers to alkynes has been developed. The reaction allows the diastereoselective synthesis of a variety of spiro compounds. Taken together, the silver catalysis and iodo trapping provides alkenyl iodides that are valuable synthons in organic synthesis and allows further functionalization by using Pd-catalyzed cross-coupling chemistry. Reactions with more complex substrates, as well as asymmetric versions of this reaction, are currently under investigation in our laboratory.



Scheme 3. Isomerization of compound **20a** into **20b** (DCE = dichloroethene).



Scheme 4. Spirocyclization of silyl enol ether **35**.

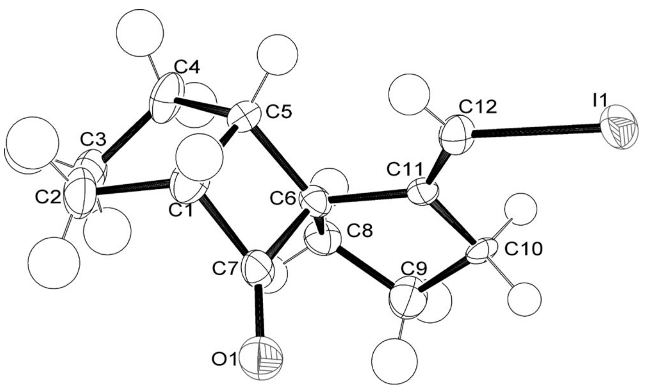
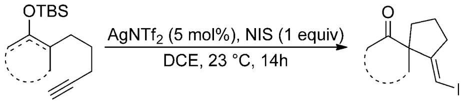
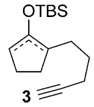
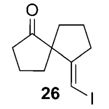
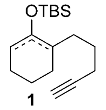
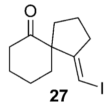
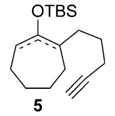
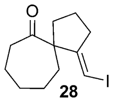
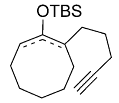
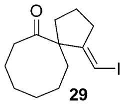
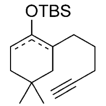
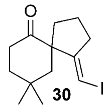
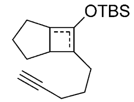
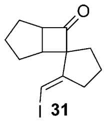
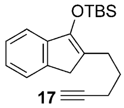
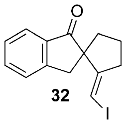
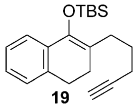
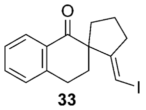
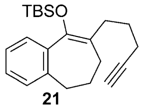
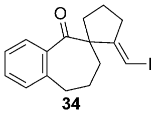


Figure 1. ORTEP diagram of tricyclic alkenyl iodide **31** with thermal ellipsoids at the 50 % probability level.[20]

Table 3. Ag-catalyzed formation of alkenyl iodides.



Entry	Substrate	Product	Yield [%]
1	 3	 26	13
2	 1	 27	68
3	 5	 28	67
4	 7	 29	81
5	 9	 30	79
6	 13	 31	54
7	 17	 32	80
8	 19	 33	78
9	 21	 34	73

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Keywords: homogeneous catalysis · silver · spiro compounds · vinyl compounds

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[20] CCDC-837001 (**31**) contains 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.

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