Heterocycle Synthesis

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Silver-Catalyzed 7-*exo*-dig Cyclization of Silylenolether-ynesulfonamides

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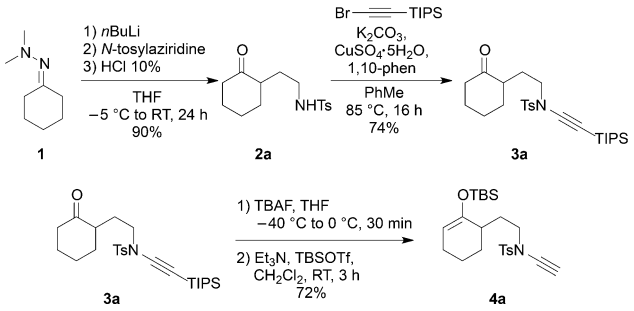
Abstract: *Cyclization of silylenolether-ynesulfonamides proceeds at ambient temperature under mild reaction conditions under silver catalysis. Bridged compounds were obtained exclusively through 7-exo-dig reactions. The protocol is applicable to a wide range of substrates, thus leading to azabicyclic frameworks.*

During the past decades, transition-metal-catalyzed cycloisomerization reactions of ene-ynamides have emerged as extraordinary tools to create molecular complexity, especially for the synthesis of nitrogen-containing heterocycles.[1,2] However, formal Conia-ene reactions of ene-ynamides are noticeably absent. Moreover, 7-*exo*-dig cyclizations using this method are exceptional because of the distal location of the nucleophilic center and the alkyne moiety.[3–5] In addition, generating a bridged bicyclic system usually requires α-disubstituted ketones to avoid concomitant formation of spiro compounds.

Herein we present a versatile, silver-catalyzed C–C bond-forming cyclization reaction of both mono- and disubstituted silylenolether-ynesulfonamides, thus leading exclusively to bridged bicyclic keto-enamides.

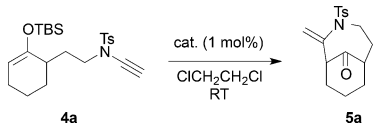
To this end, the required the silylenolether-ynesulfonamide **4a** was readily prepared by alkylation of N,N-dimethyl hydrazones with tosylaziridine[6] followed by the application of Hsung's copper-catalyzed N-alkynylation[7] reaction, thus affording the corresponding ynesulfonamide **3a** (Scheme 1). Subsequent treatment of **3a** with TBAF and subsequent addition of TBSOTf/Et_3N exclusively provided the kinetic silyloxy-ene-ynesulfonamide **4a**.[8,9]

Previously, we reported a silver-catalyzed Conia-ene cyclization of alkynyl silyl enol ethers.[4] Thus, we began our investigations by examining the cyclization of ene-ynesulfonamides using various silver and gold catalysts (Table 1). Because the kinetic silyl enol ether is formed exclusively, cyclization afforded only the bridged bicyclic compound **5a** in a short time at room temperature, and no spiro compound was observed.[10] Interestingly, the use of silver salts (entries 6–9) is as effective as gold catalysts (entry 10–11).[11] $AgNTf_2$ (entry 9) was determined to be the most efficacious catalyst to perform the 7-*exo*-dig cyclization of silylenolether-ynesulfonamides. No conversion with insoluble silver salts was observed (entries 1–4). Control experiments revealed that neither silver carbonate nor the corresponding free amide, that is, triflimic acid, were beneficial to catalyze the transformation of silyl ynesulfonamides to bridged bicyclic compounds, and a low yield was observed under metal-free conditions (entry 5). Likewise, ketones could not be transformed directly into spiro compounds. An X-ray structural



Scheme 1. Synthesis of the silyl enol ether **4a**. TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, TIPS = triisopropylsilyl, Ts = 4-toluenesulfonyl.

Table 1: Screening of catalysts.



Entry	Catalyst	*t*	Yield [%][a]
1	Ag_2CO_3	16 h	–[b]
2	AgOTs	16 h	–[b]
3	$AgCO_2Ph$	16 h	–[b]
4	AgOAc	16 h	–[b]
5	$HNTf_2$	30 min	21
6	AgOTf	30 min	90
7	$AgBF_4$	30 min	92
8	$AgSbF_6$	30 min	94
9	$AgNTf_2$	30 min	98
10	[Au(PPh$_3$)][NTf_2]	30 min	92
11	[Au(JohnPhos)(MeCN)][SbF_6]	30 min	89

[a] Yield is that of the isolated product. [b] Only the starting material was recovered.

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determination of the bridged compound **5a** provided evidence for the regioselectivity of the reaction.[12]

We next turned our attention to the effect of the solvent in this cycloisomerization reaction (Figure 1). Whereas the yield is nearly quantitative in 1,2-dichloroethane, yields decreased with the use of toluene, dichloromethane, nitromethane, and diethyl ether, and there was almost no conversion with either $CHCl_3$ or THF, and no reaction in MeCN, DMF, and MeOH, which can be attributed to the metal-coordinating properties of these solvents. Furthermore, the reaction was compatible with different electron-withdrawing groups on the nitrogen atom (Scheme 2).

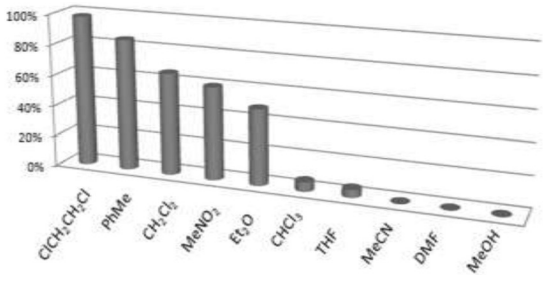
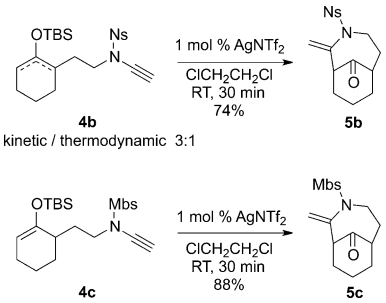


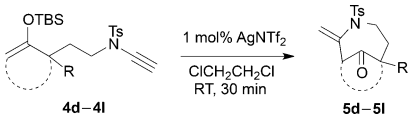
Figure 1. Screenings of solvents.

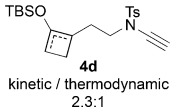
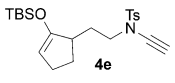
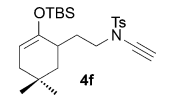
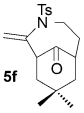
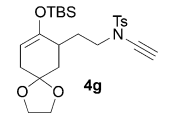
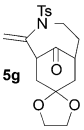
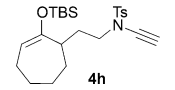
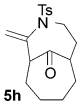
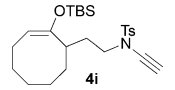
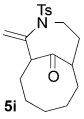
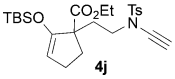
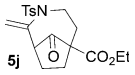
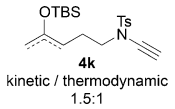


Scheme 2. Variation of the electron-withdrawing group. Mbs = *p*-methoxybenzenesulfonyl, Ns = 2-nitrobenzenesulfonyl.

With the optimal reaction conditions in hand, we examined various cyclic silyl enol ether substrates for the construction of azabicyclo[*m*.4.1] frameworks through the 7-*endo*-dig cyclization (Table 2).[13] The reaction allowed construction of a variety of ring sizes. The conformationally flexible acyclic compound **4k** as well as the strained cyclobutanone derivative **4d** led to a mixture of kinetic and thermodynamic silyl enol ethers. However cyclization could be achieved in both cases and led to original scaffolds. The functionalized ketone such **4g** could be utilized as well, thus leading to the corresponding bridged compounds with good yields. Even larger cyclic ketones, for example, seven- or eight-membered silyloxy-ynesulfonamides, were suitable compounds, thus providing the 7-*exo*-dig compounds **5h** and **5i**, respectively, in very good yields. It should be noted that an ester functional group at the bridged position was tolerated as well (entry 7).

Table 2: Cyclization using various cycloalkanones.

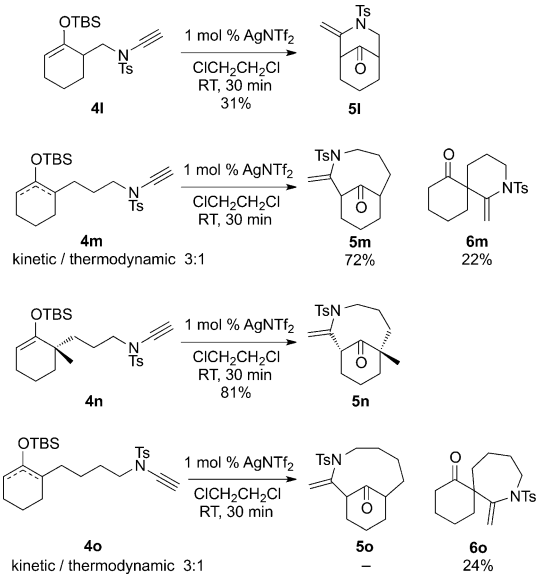


Entry	Compound	Product	Yield [%][a]
1[b]	 **4d** kinetic / thermodynamic 2.3:1	 **5d**	63
2	 **4e**	 **5e**	90
3	 **4f**	 **5f**	89
4	 **4g**	 **5g**	87
5	 **4h**	 **5h**	99
6	 **4i**	 **5i**	86
7	 **4j**	 **5j**	63
8[b]	 **4k** kinetic / thermodynamic 1.5:1	 **5k**	49

[a] Yield is that of the isolated product. [b] The compounds **4d** and **4k** were obtained as a mixture of kinetic/thermodynamic compounds.

The scope of the reaction was also investigated with respect to the spacer length (Scheme 3). Although only kinetic silyl enol ethers are obtained by shortening the spacer length, a 6-*exo*-dig cyclization afforded the adduct **5l** in a rather moderate yield. Regarding the formation of the silyl enol ether, the selectivity decreases as the ynesulfonamide function is moved further from the ketone. Although the bridged compound **5m** could still be obtained through an 8-*exo*-dig cyclization along with a small amount of the spirocompound **6m**. The homologue **4o** could not undergo 9-*exo*-dig cyclization and led only to the spirocompound **6o**. An enantiomerically enriched, disubstituted compound, bearing a three carbon linker chain (**5n**) could be obtained with a good yield.

In our pursuit of ene-ynesulfonamide cyclizations, we have focused on the influence of the substituents on the ynesulfonamide function (Table 3). The protocol was found to be general because a wide range of linear or cyclic alkyls, halogens, protected alcohols, and aromatic substituents react successfully. The reaction remained diastereoselective with



Scheme 3. Modification of the spacer length.

respect to the stereochemistry of the double bond. X-Ray crystallographic structure determinations of the bridged bicyclic compounds **5s**[14] and **5y** (Figure 2)[15] revealed a *Z*-configured *exo* double bond of the latter, and provided evidence for in situ elimination of the OBn group, thus leading to allenamide **5s**.

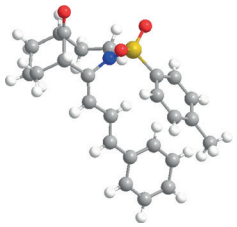
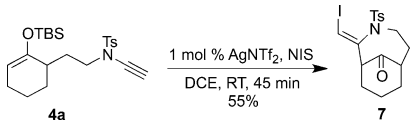


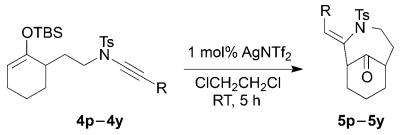
Figure 2. Crystallographic determination of **5y**.

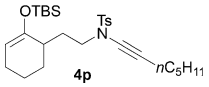
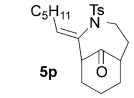
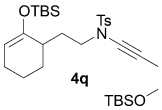
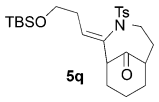
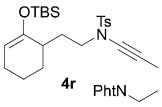
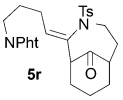
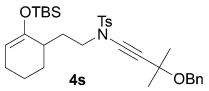
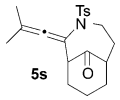
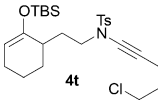
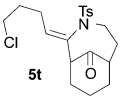
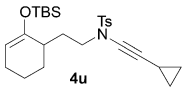
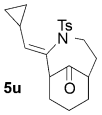
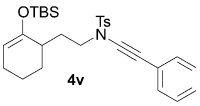
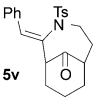
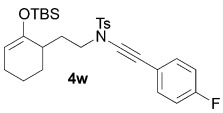
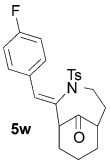
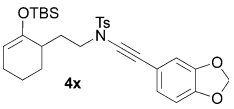
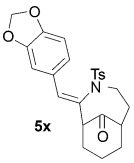
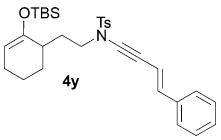
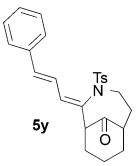
Finally, we attempted to trap the newly formed alkenylsilver intermediate species by a source of electrophilic iodine prior to protodemetalation (Scheme 4).[4,16] Thus, **4a** was treated in one pot with 1 mol% of $AgNTf_2$ and 1 equivalent of NIS in 1,2-dichloroethane, thus exclusively providing the *Z*-alkenyl iodide derivative **7** as confirmed by X-ray crystallographic structural determination.[17] It should be noted that in this case the reaction of **4a** with NIS alone led to **7** in low yield (14%).



Scheme 4. Trapping alkenylsilver intermediates. DCE = 1,2-dichloroethane, NIS = *N*-iodosuccinimide.

Table 3: Functionalization of the ynesulfonamide moiety.

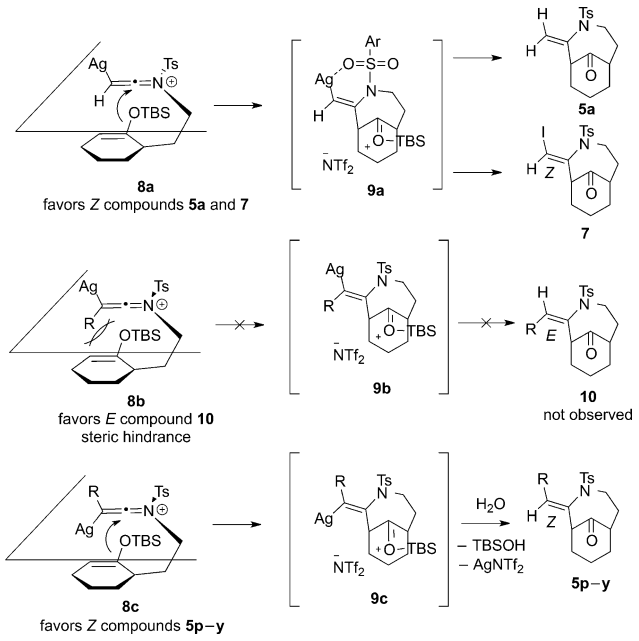


Entry	Compound	Product	Yield [%][a]
1			76
2			76
3			89
4			91
5			85
6			82
7			68
8			78
9			66
10			56

[a] Yield is that of the isolated product.

The selectivity of these reactions can be rationalized[18] by analyzing the conformations of the keteneiminium intermediates (Scheme 5). When R = H, the *Z*-configured **8a** is preferred. Thus, the six-membered silver sulfonamide-complexed ring[19] **9a** is favored and leads to **5a** by protodemetalation and to **7** by iodo-demetalation. Alternatively, when R ≠ H, the *Z*-configured compounds **5p–y** are preferred to minimize steric interactions between the R group and the ene-silyloxy-ring **8c**, thus favoring the six-membered **9c**.[20] The intermediates **9a** and **9c** are obtained by 7-*endo*-dig cyclization of **8a** and **8c**, respectively.[13]

In conclusion, the first formal conia ene cyclization of ene-ynesulfonamides has been described. Only kinetic TBS silyl enol ethers were observed, thus providing rapid access to formal 7-*exo*-dig nitrogen-containing products. A wide range



Scheme 5. Proposed mechanism.

of ynesulfonamide substituents, such as aryl, alkyls, heteroaryls, protected alcohols, halogens, and alkenes as well as various cycloalkanones are tolerated and lead to functionalized azacyclic frameworks.

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Keywords: cyclizations · heterocycles · silver · structure elucidation · synthetic methods

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[9] An X-ray structural determination of the latter clearly showed the generation of a single silyl enol ether. CCDC 1415013 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[10] DFT calculations support experimental results observed. Refer to the Supporting Information for details.
[11] Kinetics studies using $AgNTf_2$ and $[Au(PPh_3)(NTf_2)]$ have shown similar profiles for both catalysts, although the gold catalyst was faster than silver catalysis ($t_{1/2} = 2$ min for $[Au(PPh_3)(NTf_2)]$ and $t_{1/2} = 5$ min for $AgNTf_2$).
[12] CCDC 1415014 (**5a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[13] 7-*endo*-dig cyclization of keteneiminium cation is proposed although the 7-*exo-dig* compound is obtained.
[14] CCDC 1415015 (**5s**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
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