AgOTf-Catalyzed Cycloisomerization of Alkynyl Oxiranes for Dihydro-1,4-oxazine Synthesis

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Abstract: The efficient AgOTf-catalyzed isomerization reactions of various alkynyl oxiranes and alkynyl allyl alcohols were carried out at room temperature with moderate to good yields. This is an economical and mild method for the construction of O-heterocyclic compounds.

Key words: cyclization, isomerization, alkynes, epoxides, Lewis acids, silver, heterocycles, domino reaction

The activation of functional groups such as carbonyls, imines, alkenes and alkynes, through coordination with Lewis acids is a useful and important method for facilitating many different types of organic transformations. In recent years, alkyne activation with gold and platinum complexes has attracted keen interest from a number of organic chemists, because the activation brings about important molecular transformations, such as cyclization, cycloisomerization, and cycloaddition, for the synthesis of carbocyclic and heterocyclic compounds.[1] Moreover, alkynes having additional functional groups such as epoxides and aziridines[2] could be great precursors for the direct and efficient synthesis of more complex heterocycles. In order to develop this kind of intramolecular tandem cyclization, the selective reactivity of the Lewis acid to activate the alkynyl group and other groups, as well as the subsequently formed alkenyl group should be taken into consideration. Indeed, various Lewis acids can build numerous types of ring frameworks, and the outcome can depend on subtle changes in the reaction conditions.[3]

Looking through the previous results regarding the reactions of alkynyl oxiranes, cycloisomerization of alk-1-ynyl oxiranes have been the subject of intense study for highly substituted furan synthesis. There are several reports for such transformations: the KH or *t*-BuOK-catalyzed reaction via a cumulene anion,[4a] molybdenum [$Mo(CO)_5$] or ruthenium [$TpRuPPh_3(CH_3CN)Cl$]-catalyzed reaction via vinylidene intermediates,[4b,c] and gold ($AuCl_3$), platinum ($PtCl_2$) or silver (AgOTf)-catalyzed reaction via vinyl metal species.[4d–f] Among the other types of alkynyl oxiranes, alk-4-ynyl oxiranes attracted the attention of chemists because their use resulted the generation of various cyclization patterns with a wide range of metal salts. Marson et al. reported the $TiCl_4$-induced seven-membered carbocycle synthesis with the aid of 2,3-epoxy alcohol functionality, and Gansäuer and co-workers reported the [Cp_2TiCl]-catalyzed five-membered carbocycle synthesis by reductive opening to titanoxy radicals.[5] In addition, tungsten-mediated [3+2] or [3+3] cycloaddition for bicyclic lactone or pyrane synthesis was reported by Liu and co-workers, and nickel-catalyzed reductive cyclization via disfavored *endo* epoxide opening was reported by Jamison and co-workers.[6] Gold and platinum were also used in this cycloisomerization, however new C–O bonds were introduced; Shi and co-workers reported gold(I)-catalyzed cascade reactions that provided bicyclic ketals through the use of alcohol, and Fang and co-workers reported platinum(II)-catalyzed dihydro-1,4-oxazine formation reactions.[7] Our interest in metal-catalyzed domino reactions prompted us to investigate this kind of reaction. Herein, we disclose a silver-catalyzed cycloisomerization that proceeded in a distinct way to afford the dihydro-1,4-oxazines under milder conditions than those used in the first report on platinum-catalyzed reactions.

Alk-4-ynyl oxirane **1a** was chosen as the substrate for the screening of catalyst systems (Table 1). The cycloisomerization reactions were carried out at room temperature for 1 h at a concentration of 0.2 M in solvent unless otherwise specified. Employing oxophilic Lewis acid catalysts such as $BF_3{\cdot}OEt_2$, $Sc(OTf)_3$ or $Fe(OTf)_3$ afforded a mixture of allyl alcohol **3a** by E2-type ring opening and isopropyl ketone **4a** by pinacolic rearrangement,[8] indicating that these catalysts showed lower reactivities as π-activators (entries 1–3). Next, we examined silver(I) salts displaying both π-electrophilic Lewis acid character to activate the C–C multiple bond, and σ-electrophilic Lewis acid character to activate the C=X bond in the various tandem catalyses.[9] When AgOTf was used as catalyst at room temperature for 1 h (entry 4), the cycloisomerization reaction proceeded smoothly to afford dihydro-1,4-oxazine **2a** in 54% yield, and a trace amount of ketone **4a** was obtained. It is noteworthy that the dihydro-1,4-oxazine framework is found in many biologically active compounds,[10] and the previous report on the $PtCl_2$ and PPh_3AuCl-catalyzed synthesis featured reflux conditions for 24 h to afford **2a** in 62 and 50% yield, respectively.[7c] Encouraged by this result, we then screened other silver salts. Reactions with AgOTs and AgTFA having lower cationic character on Ag required elevated reaction temperature and extended reaction time (2 h; entries 5 and 6), however, the isolated yield of **2a** decreased owing to the formation of a mixture of by-products. No progress was observed in the reaction using

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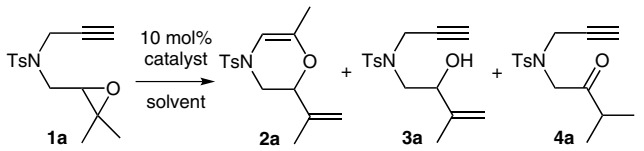
Table 1 Optimization of the Cycloisomerization of **1a**



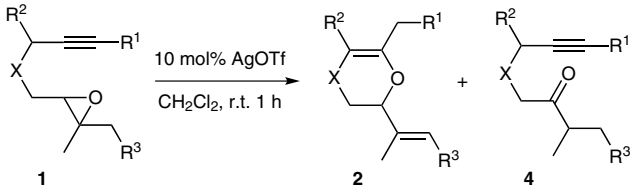
Entry	Catalyst	Solvent	Temp (°C)	Yield (%)[b]		
				2a	**3a**	**4a**
1	$BF_3{\cdot}OEt_2$	DCE	25	0	14	11
2	$Sc(OTf)_3$	DCE	25	0	46	20
3	$Fe(OTf)_3$	DCE	25	0	32	20
4	AgOTf	CH_2Cl_2	25	54	0	<5
5[c]	AgOTs	CH_2Cl_2	45	44	36	0
6[c]	AgTFA	CH_2Cl_2	45	12	10	36
7	AgOBz	CH_2Cl_2	25	0	0	0
8	$AgSbF_6$	CH_2Cl_2	25	<5	26	21
9	$AgBF_4$	CH_2Cl_2	25	<5	0	22
10	AgOTf	DCE	25	40	<5	19
11	AgOTf	MeCN	25	0	0	<5
12	AgOTf	$MeNO_2$	25	9	0	29
13	AgOTf	benzene	25	21	10	0
14	AgOTf	toluene	25	17	14	17
15[c]	*p*TsOH	toluene	120	0	0	37

[a] Reactions and conditions: alkynyl oxirane **1a** (0.25 mmol), catalyst (10 mol%), solvent (0.2 M), 1 h under N_2, unless otherwise specified.
[b] Isolated yield after chromatographic purification.
[c] Reaction ran for 2 h.

AgOBz, and $AgSbF_6$ and $AgBF_4$ gave only trace amounts of product **2a**, demonstrating that AgOTf was the most effective (entries 7–9). During solvent optimization studies (entries 10–14), other chlorinated solvents, polar solvents, and aromatic solvents were shown to provide little benefit relative to dichloroethane (DCE). On the basis of these results, we performed an acid-catalyzed control experiment with *p*TsOH, which resulted in 37% yield of **4a** even with a prolonged reaction time (2 h) under reflux conditions (entry 15).

With these optimal conditions in hand, we explored the generality of this process (Table 2). Various alkynyl oxiranes were easily prepared by epoxidation of the corresponding enynes, which were synthesized by Mitsunobu reactions with propargyl amides and allyl alcohols. The substituents on the amine group subtly affected the reactivity; several sulfonyl amides afforded the desired products **2a**–**e** in good yield (entries 1–5), regardless of having electron-withdrawing or electron-donating substituents on its phenyl ring, although the sterically hindered mesityl

Table 2 Silver(I)-Catalyzed Dihydro-1,4-oxazine Synthesis; Substrate Scope[a]



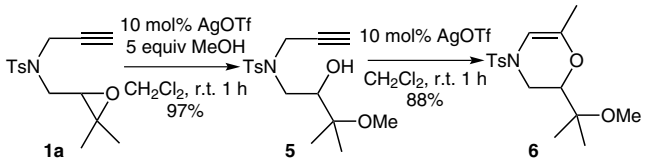
Entry	X	R^1	R^2	R^3	Product	Yield (%)[b]
1	NTs	H	H	H	**2a**	54
2	NSO_2Mes	H	H	H	**2b**	42
3	$NSO_2(4\text{-}PhC_6H_4)$	H	H	H	**2c**	55
4	$NSO_2(4\text{-}MeOC_6H_4)$	H	H	H	**2d**	47
5	$NSO_2(2\text{-}NO_2C_6H_4)$	H	H	H	**2e**	48
6	NBoc	H	H	H	**2f**	0
7	NCbz	H	H	H	**2g**	0
8	NTs	CO_2Et	H	H	**2h**	55
9[c]	NTs	Ph	H	H	**2i**	20
10[d]	NTs	Me	H	H	**2j**	33
11[e]	NTs	H	Me	H	**2k**	61
12[e]	NTs	H	H	Me	**2l**	48
13[e]	NTs	H	H	*i*Pr	**2m**	56
14	$C(CO_2Et)_2$	H	H	H	**2n**	0
15	O	H	H	H	**2o**	0

[a] Reactions and conditions: alkynyl oxirane (**1**; 0.25 mmol), catalyst (10 mol%), solvent (0.2 M), 1 h under N_2, unless otherwise specified.
[b] Isolated yield of **2** after chromatographic purification.
[c] Reaction in benzene at 80 °C for 12 h.
[d] Reaction in DCE at 50 °C for 6 h.
[e] Reaction with AgOTs in DCE at 50 °C for 12 h.

(2,4,6-trimethylphenyl) group depleted the yield to 42%. Unlike sulfonyl amide, carbamate derivatives with a Boc or Cbz group did not demonstrate any reactivity in the cycloisomerization reactions (entries 6 and 7). Next, a variety of substituents, R^1, R^2 and R^3 were evaluated. The electron-withdrawing group on the alkyne facilitated the reaction, affording compound **2h** in 55% yield, by making the β-position of the ester more electrophilic (entry 8). Other substrates possessing Ph or Me substituents on the alkyne participated in the reaction, but yielded ketone byproducts to a similar extent (**4i**, 27%; **4j**, 26%), even under heating to promote the cyclization pathway. Ketones **4i** and **4j**, which showed a more polar character than the oxazine products, could be isolated by column chromatography, and seemed not to be the assumed reaction intermediates by TLC analysis of the cycloisomerization reactions. In addition, when alkynyl oxirane **1k**, having

the methyl substituent on the propargyl position (R^2), was treated with 15 mol% AgOTs under heating, cyclized oxazine **2k** was obtained in 61% yield (entry 11), whereas treatment with AgOTf did not furnish any product, resulting in a complex mixture containing ketone **4k** as a major product. When one methyl substituent (R^3) of oxirane was changed into either an ethyl or isobutyl group (entries 12 and 13), the anticipated epoxide opening took place to afford products **2l** and **2m** in good yield under heating with AgOTs in DCE. Removing one alkyl substituent of oxirane to generate a disubstituted substrate eliminated the reactivity towards the Ag catalyst (data not shown). Switching the NTs group to $C(CO_2Et)_2$ or using an oxygen atom as a linker also led to no progress in the cycloisomerization reactions (entries 14 and 15).

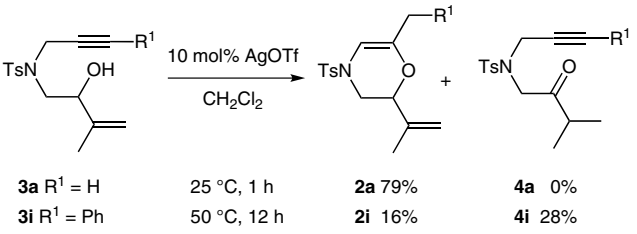
We wondered whether this interesting Ag(I)-catalyzed reaction could be successfully extended to a nucleophilic alcohol addition followed by a cyclization reaction. To test this, the reaction of alkynyl oxirane **1a** with MeOH catalyzed by 5 mol% AgOTf was carried out (Scheme 1). The formation of ring-opened alkynol **5** by selective oxirane activation followed by alcohol addition was observed to take place in high yield and subsequent cyclization by the newly formed hydroxyl group proceeded smoothly to afford dihydro-1,4-oxazine **6**. Treatment of **1a** with isopropyl or benzyl alcohol instead of methanol gave complex mixtures, and reaction with *t*BuOH resulted in the formation of **2a** (43%) without any participation of alcohol.



Scheme 1 AgOTf-catalyzed addition of alcohol nucleophile and cyclization reaction

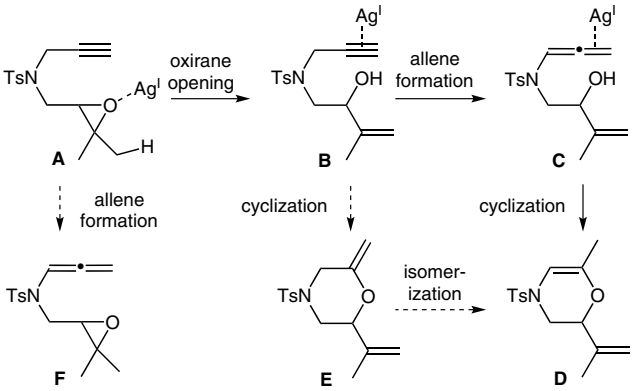
To provide insight into the cycloisomerization mechanism, we examined the Ag-catalyzed cyclization reactions of alkynyl allyl alcohols, which were supposed to be the reaction intermediates of the cycloisomerization reactions (Scheme 2).[11] Alkynyl allyl alcohol **3a**, prepared from the $Sc(OTf)_3$-catalyzed reaction of **1a**, was transformed into the corresponding product **2a** in high yield within one hour under the same reaction conditions in the presence of 10 mol% AgOTf catalyst. The cyclization reaction of **3i** resulted in the formation of **2i** (16%) with a significant amount of **4i**, which is a similar result to that obtained with the tandem cyclization reaction of **1i** shown in Table 2. The result indicates that ketone **4**, derived from allyl alcohol, does not participate in the cyclization pathway.

Based on the above experimental results, this reaction might proceed through a tandem sequence involving the first step of ring opening of oxirane (Scheme 3). Selective activation of the epoxy group in **A** by Ag(I) followed by ring opening afforded the allyl alcohol intermediate **B**.



Scheme 2 Cyclization reactions of alkynyl allyl alcohols

Subsequently, two proposed pathways are possible depending on the electrophilic C–C multiple bonds that attend the cyclization; one route proceeds through allene formation from the propargyl unit followed by cyclization of allenol **C**, whereas the second route proceeds through direct cyclization to the alkyne and sequential double bond isomerization reactions. The mechanism involving allenol **C** is considered more likely than the alternative on the basis of the following results:[7c,11b] (1) no *exo*-methylene intermediate **E** in reactions of **1h** and **1i** was observed, even though this would increase the conjugated system, and (2) the methyl substituent in **1k** did not increase the rate of cyclization.



Scheme 3 Proposed mechanism of the silver-catalyzed cycloisomerization of alkynyl oxiranes

In conclusion, we have developed a simple and economical synthetic method that can be used to obtain a range of dihydro-1,4-oxazines from alkynyl oxiranes and alkynyl allyl alcohols.[12] The cycloisomerization reactions were performed with the AgOTf catalyst under mild conditions and were successfully extended to the addition of alcohol followed by cyclization. Efficient domino reactions using various functional groups such as C–C multiple bonds and versatile three-membered heterocycles are currently being investigated.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **AgOTf-Catalyzed Cycloisomerization of Alkynyl Oxiranes for Dihydro-1,4-oxazine Synthesis; Typical Procedure:** Alkynyl oxirane **1a** (0.25 mmol) in anhydrous CH_2Cl_2 (0.2 M) was treated with a catalytic amount of AgOTf (10 mol%). The reaction mixture was stirred for 1 h at room temperature under a N_2 atmosphere. The progress of the reaction was monitored by TLC and, upon completion, the reaction mixture was concentrated and purified by silica gel column chromatography to afford the pure product **2a** in 54% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.4 Hz, 2 H), 7.34 (d, *J* = 8.1 Hz, 2 H), 5.84 (s, 1 H), 4.93 (s, 1 H), 4.88 (s, 1 H), 3.82 (d, *J* = 12.8 Hz, 1 H), 3.31 (d, *J* = 9.0 Hz, 1 H), 2.83 (dd, *J* = 13.5, 9.3 Hz, 1 H), 2.44 (s, 3 H), 1.78 (s, 3 H), 1.64 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.9, 140.8, 140.4, 133.3, 129.8, 127.4, 113.4, 99.4, 74.3, 46.4, 21.6, 18.4, 17.8; HRMS (FAB): *m*/*z* [M^+] calcd for $C_{15}H_{19}NO_3S$: 293.1086; found: 293.1035.

