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Selective Transformation of *N*-(Propargylic)hydroxylamines into 4-Isoxazolines and Acylaziridines Promoted by Metal Salts

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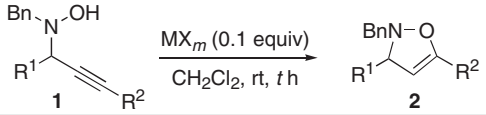
Cyclization of *N*-(propargylic)hydroxylamines catalyzed by $AgBF_4$ afforded the corresponding 4-isoxazolines in good yields. Copper salts were found to promote the further transformation to acylaziridines. The combined use of $AgBF_4$ and CuCl realized direct transformation of *N*-(propargylic)-hydroxylamines into *cis*-acylaziridines.

Compounds bearing a 4-isoxazoline ring have biological activities and are versatile synthetic intermediates for nitrogen-containing chemicals.[1] 1,3-Dipolar cycloaddition of nitrones to acetylenes is one of the most attractive approaches to the synthesis of 4-isoxazolines, however, the method often suffers from poor regioselectivity.[1] Conjugate addition of hydroxylamines to α,β-unsaturated carbonyl compounds followed by dehydration is an alternative way.[1] 4-Isoxazolines could be also prepared via ring-closure of *N*-(propargylic)hydroxylamines catalyzed by zinc, palladium, or gold salt in the presence of an amine.[2] Furthermore, direct ring-closure of zinc salts of *N*-(propargylic)hydroxylamines, generated in situ by addition of alkynylzinc reagents to nitrones with an ester or amide group, has been reported.[3] Recently, we have reported a one-pot reaction consisting of an enantioselective nucleophilic addition of alkynylzinc reagents to nitrones and a subsequent cyclization to give the corresponding (*S*)-4-isoxazolines with excellent enantioselectivity.[4] However, the cyclization step was quite slow even when excess amounts of dimethylzinc were added for the promotion. In order to prepare 4-isoxazolines more efficiently, the cyclization of *N*-(propargylic)hydroxylamines to 4-isoxazolines was investigated in the presence of a metal salt. Herein, we wish to describe our finding that $AgBF_4$ was an efficient catalyst for the cyclization and further addition of a copper salt could rearrange the 4-isoxazolines to the corresponding acylaziridines. Direct stereoselective generation of *cis*-acylaziridines from *N*-(propargylic)hydroxylamines was also achieved with a $AgBF_4$–CuCl combined system.

First, the cyclization of *N*-benzyl-*N*-(1,3-diphenylprop-2-ynyl)hydroxylamine (**1a**) was examined in the presence of a catalytic amount of metal salt without an amine in CH_2Cl_2 at rt as shown in Table 1. It was reported that ZnI_2 and $PdCl_2$ promoted the cyclization in the presence of an amine base.[2a,2b] Although ZnI_2 was not a suitable catalyst for the cyclization in the absence of the base (Entry 1), $PdCl_2$ promoted the cyclization to give the corresponding 4-isoxazoline in 86% yield after 17 h (Entry 2). $PtCl_2$ was not as effective as $PdCl_2$ (Entry 3). It was found that silver salts also promoted the cyclization (Entries 4–6). Cationic silver salts were more effective and the cyclization was completed within 4 h by using $AgBF_4$, rather faster than $PdCl_2$, to give 4-isoxazoline **2a** in 89% yield (Entry 6). Activity of $AuCl_3$ for the cyclization was high, but unknown by-products

Table 1. Cyclization of **1** in the presence of a metal salt



Entry	R^1	R^2	**1**	MX_m	*t*/h	Yield/%
1	Ph	Ph	**a**	ZnI_2	23	39
2				$PdCl_2$	17	86
3				$PtCl_2$	42	—[a]
4				$AgNO_3$	40	57
5				AgOTf	21	84
6				$AgBF_4$	4	89
7				$AuCl_3$	0.3	61
8				$AuCl_3$	22	74
9	Ph	*n*-Hex	**b**	$AgBF_4$	8	73
10	Ph	*t*-Bu	**c**	$AgBF_4$	22	82
11	*n*-Pr	Ph	**d**	$AgBF_4$	8	53[b]
12				$AgBF_4$[c]	8	64
13	*c*-Hex	Ph	**e**	$AgBF_4$	6	85
14	Me	*n*-Hex	**f**	$AgBF_4$	8	70

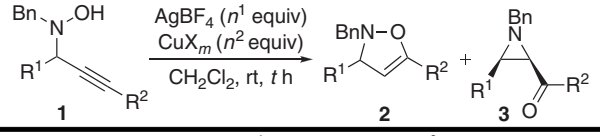
[a]Most of the hydroxylamine **1a** was recovered. [b]The hydroxylamine **1d** was recovered in 14% yield. [c]The amount of $AgBF_4$ was 0.2 equiv.

were produced lowering the chemical yield of **2a** (Entries 7 and 8). Thus we chose readily available $AgBF_4$ (0.1 equiv) as the catalyst for the cyclization of several other *N*-(propargylic)-hydroxylamines **1b**–**1f** and the corresponding 4-isoxazolines **2b**–**2f** were obtained in good to high chemical yields (Entries 9–14). In the case of **1d**, the use of 0.2 equiv of $AgBF_4$ improved the chemical yield (Entry 12).

During the survey of metal salts for the cyclization of **1a**, it was found that not only 4-isoxazoline **2a** but also a *cis*-acylaziridine **3a**[5f,6] was produced with complete diastereoselectivity when CuCl was used (Table 2, Entry 1). Although the transformation of 4-isoxazolines to acylaziridines had been reported,[1,5] the conditions were drastic and the diastereoselectivity was not always good.

Next, direct transformation of **1a** to acylaziridine **3a** was intensively investigated (Table 2). By the use of cationic copper salts, the *cis*-acylaziridine **3a** was obtained as a major product (Entries 4–7). However, the reaction was messy and chemical yield was not satisfactory. In order to accelerate the cyclization step, a catalytic amount of $AgBF_4$ was added. Among copper salts examined, CuCl was most effective in the presence of $AgBF_4$ as a co-catalyst (Entries 9 and 13–16). By the use of 0.2 equiv of $AgBF_4$ and 1.0 equiv of CuCl, **3a** was finally obtained in 88% yield (Entry 10). When the amount of CuCl was

Table 2. Direct transformation of **1** to **3**



Entry	R^1	R^2	**1**	n^1 /equiv	CuX_m	n^2 /equiv	t /h	**2** /%	**3** /%
1	Ph	Ph	**a**	0	CuCl	1.0	41	16	2[a]
2				0	$CuCl_2$	1.0	44	—	—
3				0	CuI	1.0	44	—	—[b]
4				0	CuOTf[c]	1.0	17	23	58
5				0	$Cu(OTf)_2$	1.0	48	—	45
6				0	$CuBF_4$[d]	1.0	7	—	45
7				0	$Cu(BF_4)_2$	1.0	25	—	48
8				0.1	CuCl	1.0	8	32	61
9				0.2	CuCl	1.0	8	13	84
10				0.2	CuCl	1.0	20	4	88
11				0.2	CuCl	0.2	8	10	58
12				0.2	CuCl	0.2	23	—	82
13				0.2	CuOTf[c]	1.0	7	—	35
14				0.2	$Cu(OTf)_2$	1.0	8	—	13
15				0.2	$CuBF_4$[d]	1.0	8	—	42
16				0.2	$Cu(BF_4)_2$	1.0	8	10	42
17	Ph	*n*-Hex	**b**	0.2	CuCl	1.0	27	—	63
18	Ph	*t*-Bu	**c**	0.2	CuCl	1.0	24	—	72[e]
19	*n*-Pr	Ph	**d**	0.2	CuCl	1.0	41	—	49[e,f]
20	*c*-Hex	Ph	**e**	0.2	CuCl	1.0	25	14	64
21				0.3	CuCl	1.0	24	7	76
22	Me	*n*-Hex	**f**	0.2	CuCl	1.0	23	—	58

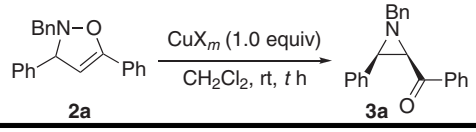
[a]The hydroxylamine **1a** was recovered in 69% yield. [b]Most of the hydroxylamine **1a** was recovered. [c]$CuOTf(C_6H_6)_{0.5}$. [d]$CuBF_4(CH_3CN)_4$. [e]The corresponding *trans*-isomer of **3** was obtained in 6% (Entry 18) and in 10% (Entry 19) yields, respectively. [f]An imine, *N*-(1-phenylhex-1-yn-3-ylidene)-benzylamine (**4d**), was obtained in 28% yield.

decreased to 0.2 equiv, the transformation proceeded a little sluggishly to afford **3a** still in high yield (Entries 11 and 12). The one-pot cyclization–isomerization was applied to several other *N*-(propargylic)hydroxylamines **1b**–**1f** in the presence of $AgBF_4$ (0.2 equiv) and CuCl (1.0 equiv) to afford the corresponding *cis*-acylaziridines **3b**–**3f** (Entries 17–22).[6] In the case of *cis*-pivaloylaziridine **3c**, a small amount of *trans*-isomer was formed (Entry 18). Transformation from **1d** was not so clean and formation of the corresponding *trans*-isomer and a dehydrated imine **4d** was also observed (Entry 19). In the case of **1e**, increase of the amount of $AgBF_4$ could improve the chemical yields (Entries 20 and 21).

To confirm that copper salt promotes transformation of the 4-isoxazoline into the acylaziridine, 4-isoxazoline **2a** was treated with copper salts (Table 3). Although the reaction was rather sluggish when CuCl was used (Entry 1), $CuOTf(C_6H_6)_{0.5}$ realized high chemical yield (Entry 2).

Finally, when the optically active **1a** (99% ee) was subjected to the present reactions under the same conditions as those of Entry 6 in Table 1 and Entry 10 in Table 2, the optically active **2a** (92%, 98% ee) and **3a** (87%, 98% ee) were obtained without loss of optical purities, respectively.

Table 3. Transformation of **2a** to **3a** promoted by a copper salt



Entry	CuX_m	t/h	Yield/%
1	CuCl	41	23[a]
2	$CuOTf(C_6H_6)_{0.5}$	4	81
3	$Cu(OTf)_2$	41	3
4	$CuBF_4(CH_3CN)_4$	22	71
5	$Cu(BF_4)_2$	41	45

[a]The 4-isoxazoline **2a** was recovered in 68% yield.

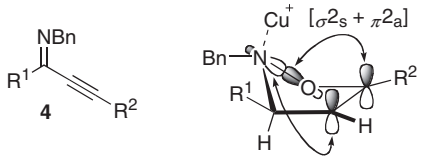


Figure 1.

Although the precise reaction mechanism is not yet clear, a radical mechanism might be ruled out, since addition of galvinoxyl free radical in the reaction of **1a** to **2a** (according to Entry 6 in Table 1) or **2a** to **3a** (according to Entry 2 in Table 3) as a radical inhibitor did not affect the reaction.[7–9]

In the transformation of 4-isoxazoline to acylaziridine, [1,3]-sigmatropic rearrangement is a possible pathway to afford the *cis*-aziridine (Figure 1).[5c–5e] Copper salt might activate the reaction via coordination by nitrogen resulting in lowering the LUMO energy of the N–O bond.

As described above, a convenient one-pot transformation of *N*-(propargylic)hydroxylamines into the corresponding 4-isoxazolines and aziridines, which are useful synthons for the synthesis of nitrogen-containing biologically active compounds, has been developed.[1,10] Further studies on this reaction are in progress in our laboratory.

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6 The *cis*-stereochemistry of **3a**–**3f** was confirmed by the coupling constant J_{2-3} (6.4–7.4 Hz) between the methine protons in aziridine rings.[5]

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8 When **2a** was treated with 1.0 equiv of $CuOTf(C_6H_6)_{0.5}$ in $ClCH_2CH_2Cl$ at 80 °C for 0.5 h, **3a** was obtained in 80% yield and diastereoselectivity was still high (**3a**/*trans*-isomer = 20/1, determined by ^1H NMR spectrum of the crude products) different from the result of the similar reaction promoted by $Co_2(CO)_8$ (0.5 equiv), in which *cis*/*trans* isomers' ratio was 2.8/1.[5f] This fact might suggest that the present reaction does not proceed through a radical pathway via the metal enolate–aza radical intermediate as proposed in ref. 5f.

9 When the direct transformation of **1a** to **3a** according to Entry 10 in Table 2 was performed in the presence of galvinoxyl free radical (1.2 equiv), the reaction proceeded sluggishly to give **3a** in 10% yield accompanied by the production of an imine, *N*-(1,3-diphenylprop-2-ylidene)-benzylamine (**4a**) (34%). Galvinoxyl free radical might oxidize CuCl to give more Lewis acidic Cu(II) species, which promoted the dehydration of **1a**.

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