Copper-Catalyzed Skeletal Rearrangement of *O*-Propargylic Aryloximes into Four-Membered Cyclic Nitrones – Chirality Transfer and Mechanistic Insight

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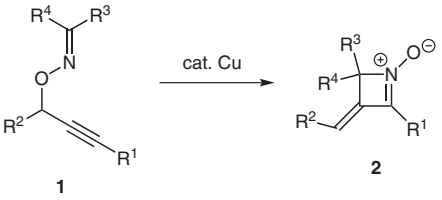
Abstract: Copper-catalyzed skeletal rearrangement of *O*-propargylic aryloximes (*E*)-**1** were carried out to afford the corresponding four-membered cyclic nitrones **2** in good to excellent yields. The optimal reactions conditions of the highly regioselective reactions involved the use of $[CuCl(cod)]_2$ in acetonitrile at 70 °C. In the case of (*Z*)-**1**, however, the reaction proceeded in the absence of the copper catalysts to afford the identical compound **2** in good yields. Furthermore, the reactions were also carried out using chiral substrates (*R*)-**1** in the presence of Cu catalysts to afford (*R*)-**2** with good levels of chirality transfer.

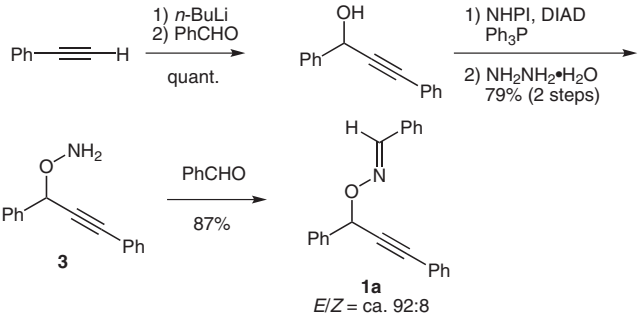
Key words: copper, skeletal rearrangement, oxime, nitrone, chirality transfer

Skeletal rearrangements that are catalyzed by π-acidic metal complexes have served as one of the most attractive transformations due to the effective cleavage of σ-bonds such as carbon–carbon, carbon–heteroatom, or heteroatom–heteroatom bonds.[1] For the catalytic skeletal rearrangements, dramatic substitution effects leading to diverse molecular skeletons are often observed. Moreover, the reactions can be carried out under mild conditions using readily accessible starting materials to afford highly elaborate molecules that remain elusive using conventional synthetic methods. Investigations of such catalytic skeletal rearrangements have mainly focused on 1,*n*-enynes[2] and propargylic esters[3] as substrates. Recently, we have found that *O*-propargylic oximes can act as novel substrates for the π-acidic metal-catalyzed skeletal rearrangements in providing various heterocyclic compounds.[4] Specifically, we reported that the copper-catalyzed skeletal rearrangement of (*E*)-*O*-propargylic aryloximes **1** afforded the corresponding four-membered cyclic nitrones **2** in good to excellent yields with high regioselectivities (Scheme 1).[4a,5,6] Herein, we describe the full scope of the copper-catalyzed skeletal rearrangement of *O*-propargylic aryloximes **1**, including the thermal rearrangement of (*Z*)-**1** in the absence of the copper catalysts. Moreover, the copper-catalyzed reaction of chiral substrates (*R*)-**1** afforded (*R*)-**2** with good levels of chirality transfer.



Scheme 1 Formation of cyclic nitrones **2**

As illustrated in Scheme 2, the *O*-propargylic aryloxime substrate **1a** was readily prepared via three steps: 1) alkynylation of benzaldehyde, 2) Mitsunobu reaction with *N*-hydroxyphthalimide (NHPI), along with in situ removal of the phthaloyl group using hydrazine, and 3) condensation of corresponding propargyloxyamine **3** with benzaldehyde to afford a 92:8 mixture of isomers (*E*)-**1a** and (*Z*)-**1a** (readily separated by silica gel column chromatography).



Scheme 2 Preparation of substrate **1a**

In the case of substrate (*E*)-**1a**, which possesses phenyl groups at the alkyne terminus, the propargylic position, and the oxime moiety, the reaction was carried out in the presence of CuBr (10 mol%) in toluene at 100 °C for 42 hours to afford the corresponding four-membered cyclic nitrone (*E*)-**2a** in 96% yield (Table 1, entry 1). Although CuCl also exhibited comparable catalytic activity, the use of CuI was not very effective (entries 2 and 3, respectively). The use of $PtCl_2$ and InCl gave (*E*)-**2a** in lower yields (entries 4 and 5, respectively), whereas the use of AuCl, $AuCl_3$, and AgOTf resulted in the decomposition of (*E*)-**1a** (entries 6–8, respectively). Brønsted acids, such as TfOH, did not help in promoting the reaction (entry 9). In the absence of the Cu catalysts, the reaction of (*E*)-**1a** at 100 °C did not proceed; in fact, (*E*)-**1a** was recovered

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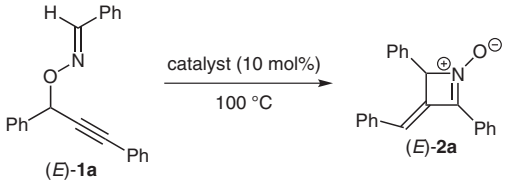
quantitatively (entry 10). Among the various solvents used, toluene, 1,4-dioxane, and THF gave (*E*)-**2a** in good yields (entries 1, 11, and 12, respectively). Interestingly, although faster reactions times were observed using polar solvents such as acetonitrile and DMF, the yields were lower than that using toluene (entries 14 and 15, respectively). The use of a protic solvent such as ethanol resulted in rapid decomposition of the starting material (*E*)-**1a** (entry 16).

Table 1 Catalytic Activities for the Reactions of (*E*)-**1a**

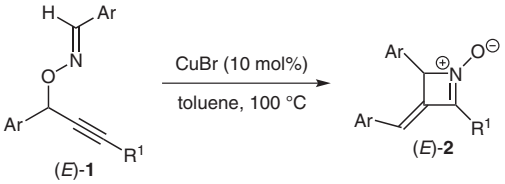


Entry	Catalyst	Solvent	Time (h)	Yield (%)[a]	Recovery of **1a** (%)[a]
1	CuBr	toluene	42	96[b]	<1
2	CuCl	toluene	23	91	<1
3	CuI	toluene	43	41	54
4	$PtCl_2$	toluene	12	34	<1
5	InCl	toluene	33	42	<15
6	AuCl	toluene	15	<1	<1
7	$AuCl_3$	toluene	15	<1	<1
8	AgOTf	toluene	2	<1	<1
9	TfOH	toluene	24	<1	36
10	none	toluene	24	<1	>99
11	CuBr	1,4-dioxane	11	93	<1
12	CuBr	THF	11	93	<1
13	CuBr	hexane	26	75	16
14	CuBr	MeCN	3.5	82	<1
15	CuBr	DMF	2.5	62	<1
16	CuBr	EtOH	2	<1	<1

[a] Determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.
[b] Isolated yield.

The conditions as described above (Table 1, entry 1) were employed for the reactions of substrates (*E*)-**1b**–**m**, which possess identical substituents at the propargyl (R^2) and the oxime (R^3) positions (cf. Scheme 1, Table 2). The reaction of aryl substrates **1b**, **1c**, **1d**, and **1e** afforded the *E*-isomer as the sole product (entries 1–4, respectively), whereas the reaction of substrates **1f**, **1g**, and **1h**, which contain an alkyl group at R^1, formed the corresponding *Z*-isomer as a by-product (entries 5–7). A bulky *tert*-butyl group disrupted the reaction (entry 8). The terminal alkyne group of **1j** quickly decomposed under the reaction conditions (entry 9). A 4-(trifluoromethyl)phenyl group at the propargylic position decreased the reaction rate, whereas a *p*-anisyl group at the propargylic position and the oxime moiety completely inhibited the reaction (entries 10, 11, respectively).

Table 2 Copper-Catalyzed Reactions of (*E*)-**1b**–**m**[a]



Entry	**1**	R^1	Ar	Time (h)	**2**	Yield (%)[b]
1	**1b**	4-$F_3CC_6H_4$	Ph	16	**2b**	92
2	**1c**	4-ClC_6H_4	Ph	24	**2c**	85
3	**1d**	4-MeC_6H_4	Ph	29	**2d**	94
4	**1e**	4-$MeOC_6H_4$	Ph	39	**2e**	83
5	**1f**	*n*-Pr	Ph	10	**2f**	80[c]
6	**1g**	H_2C=$CHCH_2$	Ph	12	**2g**	63[d]
7	**1h**	*c*-C_6H_{11}	Ph	18	**2h**	80[e]
8	**1i**	*t*-Bu	Ph	72	–	n.r.
9	**1j**	H	Ph	14	–	–[f]
10	**1k**	Ph	4-$F_3CC_6H_4$	67	**2k**	61
11	**1l**	Ph	4-$MeOC_6H_4$	14	–	–[f]
12	**1m**	4-MeC_6H_4	4-MeC_6H_4	20	**2m**	81

[a] The reaction of (*E*)-**1** (0.4 mmol) was carried out in the presence of CuBr (10 mol%) in toluene (0.8 mL) at 100 °C.
[b] Isolated yield; n.r. = no reaction.
[c] An 81:19 mixture of the *E*- and *Z*-isomers was obtained.
[d] A 78:22 mixture of the *E*- and *Z*-isomers was obtained.
[e] A 93:7 mixture of the *E*- and *Z*-isomers was obtained.
[f] Decomposition of the starting material.

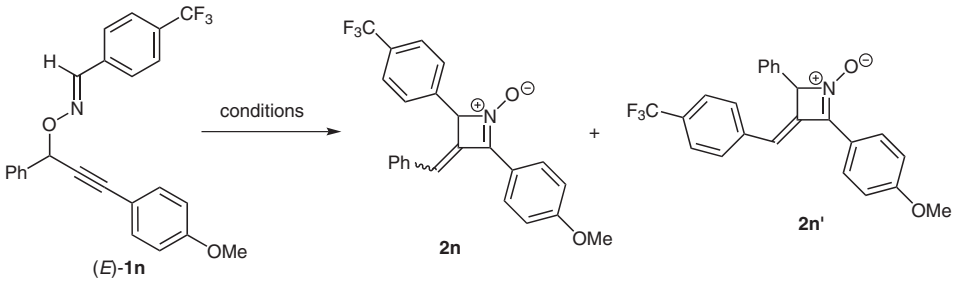
In the case of substrate (*E*)-**1n**, the reaction formed a 68:32 mixture of regioisomers **2n** and **2n′** (combined yield: 96%; Table 3, entry 2), which corresponded to the switched positions of the substituents between the olefinic moiety and the sp^3 carbon of four-membered ring, and the substituent at the olefinic moiety of the major regioisomer **2n** was derived from that at propargylic position of the substrate. In order to improve the regioselectivity, the reaction conditions were re-examined, as summarized in Table 3. Although copper(I) salts, such as CuCl, CuBr, CuI, and CuOAc were less reactive and required longer reaction times to completely consume the starting material (entries 1–4, respectively), copper(II) salts such as $CuCl_2$ and $Cu(OAc)_2$ resulted in significant decomposition of the starting substrate (entries 5 and 6, respective-

ly). Among the copper complexes, $[CuCl(cod)]_2$ exhibited favorable catalytic activity for the present reaction (entries 9 and 11–14). Furthermore, the regioselectivity was significantly affected by the reaction solvent – in particular, the use of acetonitrile gave **2n** with high regioselectivity (entry 13). Moreover, excellent regioselectivity was attained by conducting the reaction at 70 °C (entry 14). The use of other transition metals, such as $PtCl_2$ and InCl, was not effective, even in acetonitrile (entries 15 and 16, respectively).

Subsequently, the optimal conditions (Table 3, entry 14) were employed for the reactions of the remaining (*E*)-**1** substrates, as summarized in Table 4. Substrates (*E*)-**1n**,**o**,**p**, which possess an electron-rich aromatic moiety at the alkyne terminus, afforded products with high regioselectivities (Table 4, entries 1–3, respectively) – in particular, bulky substituents at the R^1 position selectively formed the *E*-isomer (entries 2 and 3). In contrast, substrate (*E*)-**1r**, which possesses an electron-deficient 4-(trifluoromethyl)phenyl group, resulted in products with lower regioselectivity (entry 5). Substrates (*E*)-**1s** and (*E*)-**1t**, which possess an alkyl group at the alkyne terminus, afforded nitrones **2s** and **2t** (entries 6 and 7, respectively) in excellent yields with high regioselectivities.

Substrates with an alkyl group at the propargylic position (R^2) required elevated reaction temperatures (100 °C) to form the desired products in good yields (Table 5, entries 1 and 2). As a note, the reaction of substrate (*E*)-**1x**, which possesses a *p*-anisyl group as its oxime moiety, did not form the desired product due to the decomposition of the starting compound (entry 4). The reaction of ketoxime **1y** afforded the corresponding product **2y** in a moderate yield (Scheme 3) – interestingly, (*Z*)-**2y** was obtained as the major isomer.

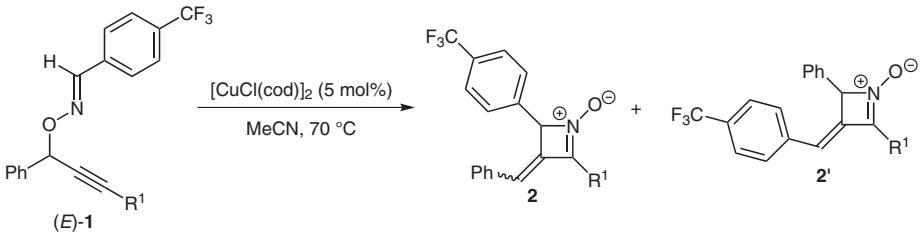
Table 3 Optimization of Reaction Conditions



Entry	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[a]	**2n**/**2n′**	*E*/*Z* of **2n**
1	CuCl (10)	toluene	100	24	94	70:30	>99:1
2	CuBr (10)	toluene	100	42	96	68:32	>99 :1
3	CuI (10)	toluene	100	48	18	72:28	>99:1
4	CuOAc (10)	toluene	100	27	91	85:15	84:16
5	$CuCl_2$ (10)	toluene	100	4	32	93:7	>95:5
6	$Cu(OAc)_2$ (10)	toluene	100	45	45	67:33	>98:2
7	$[Cu(OTf)]_2$·toluene (5)	toluene	100	22	<1[b]	–	–
8	$CuBr(PPh_3)_3$ (10)	toluene	100	48	23	69:31	>99:1
9	$[CuCl(cod)]_2$ (5)	toluene	100	7	quant	73:27	90:10
10	$[CuBr(cod)]_2$ (5)	toluene	100	6	85	94:6	76:24
11	$[CuCl(cod)]_2$ (5)	CH_2Cl_2	100	4.5	quant	81:19	78:22
12	$[CuCl(cod)]_2$ (5)	1,4-dioxane	100	7	46	82:18	84:16
13	$[CuCl(cod)]_2$ (5)	MeCN	100	3	(90)	87:13	80:20
14	$[CuCl(cod)]_2$ (5)	MeCN	70	14	99 (92)	98:2	74:26
15	$PtCl_2$ (10)	MeCN	100	9.5	24	>98:2	>98:2
16	InCl (10)	MeCN	100	41	28	82:18	>98:2

[a] Combined yield of **2n** and **2n′**. The yield and ratio were determined using ^1H NMR spectroscopy with CH_2Br_2 as an internal standard. Isolated yield in parentheses.
[b] Decomposition of (*E*)-**1n**.

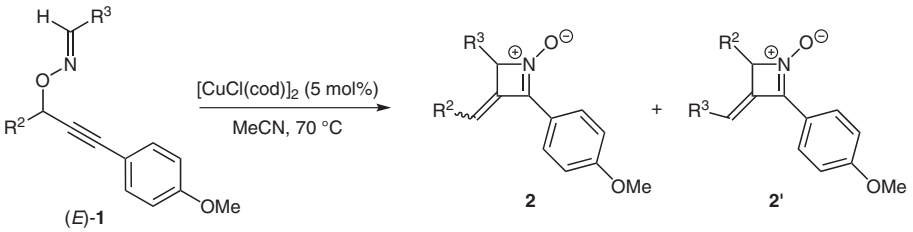
Table 4 Copper-Catalyzed Reactions of (*E*)-**1n–t**[a]



Entry	**1**	R^1	Time	**2**	Yield (%)[b]	**2/2′**	*E*/*Z* of **2**
1	**1n**	4-$MeOC_6H_4$	16 h	**2n**	92	98:2	74:26
2	**1o**	2-$MeOC_{10}H_6$	4 d	**2o**	82	95:5	97:3
3	**1p**	2,6-$(MeO)_2C_6H_3$	4 d	**2p**	91	99:1	95:5
4	**1q**	Ph	24 h	**2q**	86	94:6	73:27
5	**1r**	4-$F_3CC_6H_4$	48 h	**2r**	89	91:9	74:26
6	**1s**	*n*-Pr	36 h	**2s**	91	97:3	73:27
7	**1t**	*c*-C_6H_{11}	7 d	**2t**	95	93:7	83:17

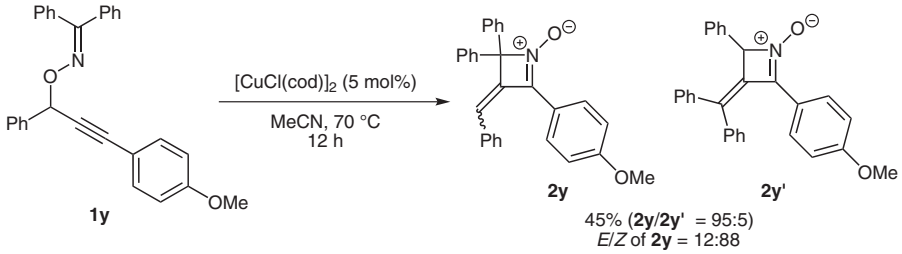
[a] The reaction of (*E*)-**1** (0.4 mmol) was conducted in the presence of $[CuCl(cod)]_2$ (5 mol%) in MeCN (0.8 mL) at 70 °C.
[b] Combined yield of **2** and **2′**. The ratio was determined using ^{1}H NMR spectroscopy.

Table 5 Copper-Catalyzed Reactions of (*E*)-**1u–x**[a]

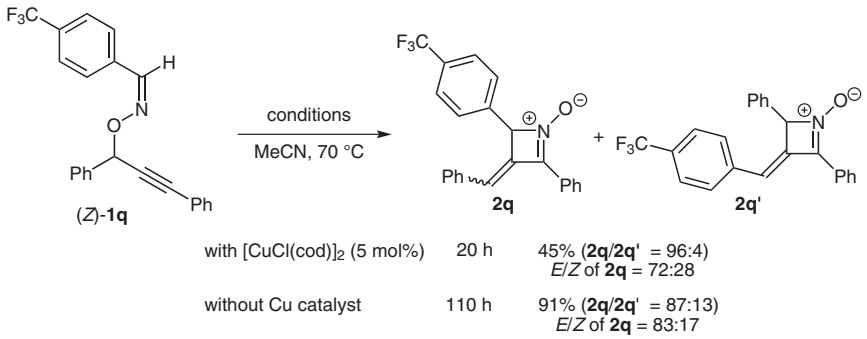


Entry	**1**	R^2	R^3	Time (h)	**2**	Yield (%)[b]	**2/2′**	*E*/*Z* of **2**
1[c]	**1u**	*n*-Pr	4-$F_3CC_6H_4$	24 h	**2u**	77	98:2	73:27
2[c]	**1v**	*i*-Pr	4-$F_3CC_6H_4$	25 h	**2v**	71	95:5	74:26
3	**1w**	Ph	2-naphthyl	18 h	**2w**	88	97:3	74:26
4	**1x**	Ph	*p*-anisyl	16 h	–	nd	–	–

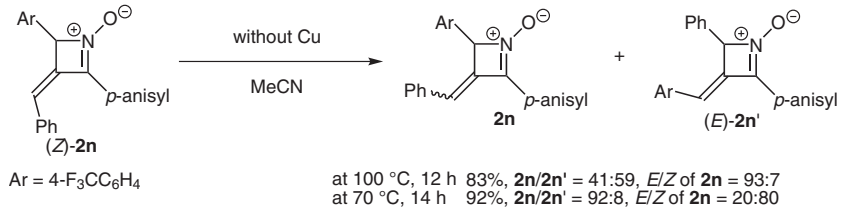
[a] The reaction of (*E*)-**1** (0.4 mmol) was conducted in the presence of 5 mol% of $[CuCl(cod)]_2$ in MeCN (0.8 mL) at 70 °C.
[b] Combined yield of **2** and **2′**. The ratio was determined using ^{1}H NMR spectroscopy. nd = not detected.
[c] At 100 °C.



Scheme 3 Cyclization of ketoxime **1y**



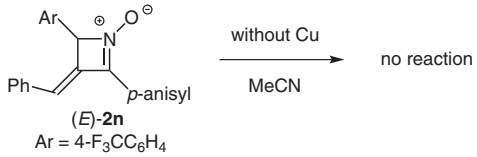
Scheme 4 Cyclization reaction of (*Z*)-**1q**



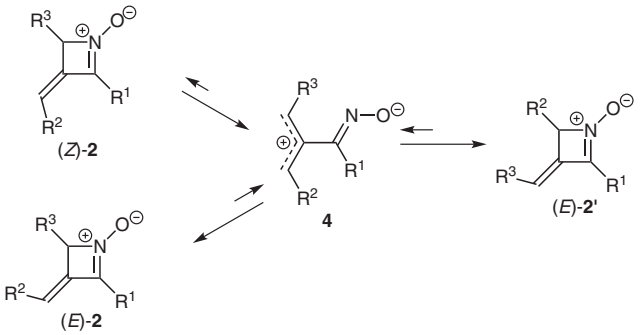
Scheme 5 Isomerization of (*Z*)-**2n**

In the presence of $[CuCl(cod)]_2$, both the reactions of (*Z*)-**1q** and (*E*)-**1q** (Scheme 4) afforded **2q**. In the absence of copper catalysts, however, only the reaction of (*Z*)-**1q** formed **2q**, but required a longer reaction time.

The isomerization experiments were further examined to gain insight into the mechanism of the reactions. Product (*Z*)-**2n**, albeit a minor product, was successfully converted to (*E*)-**2n** and (*E*)-**2n′** in the absence of Cu catalysts at 100 °C. However, the conversion did not occur at a lower reaction temperature of 70 °C (Scheme 5). In contrast, (*E*)-**2n** remained unchanged, even at 100 °C (Scheme 6).[7] These results strongly suggest that only the *Z*-isomer can undergo isomerization, and help explain the higher regioselectivity and lower *E*/*Z* selectivity of the reaction of (*E*)-**1n** under lower reaction temperatures (70 °C rather than 100 °C) (Table 3, entries 13 and 14). We believe that the isomerization of (*Z*)-**2** to (*E*)-**2** and (*E*)-**2′** proceeds through cleavage and reformation of the sp^3 carbon–nitrogen bond via zwitterionic intermediate **4**, which possesses an allylic cation moiety (Scheme 7). Presumably, the relaxation of the 1,3-allylic strain between R^1 and R^2 within (*Z*)-**2** helps drive the ring-opening step. Accordingly, the low regioselectivity of substrate (*E*)-**1r** can be explained as the stabilization of the anionic moiety of intermediate **4** due to the electron-withdrawing 4-(trifluoromethyl)phenyl group at R^1 that facilitates the isomerization to the minor regioisomer **2r′**, even at 70 °C (Table 4, entry 5).



Scheme 6 Attempted isomerization of (*E*)-**2n**

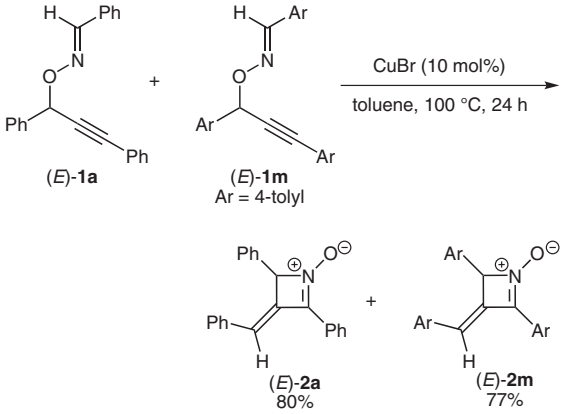


Scheme 7 Isomerization of (*Z*)-**2** through zwitterionic intermediate **4**

Moreover, the results of our ^{13}C-labeling experiments (Scheme 8) are in agreement with the isomerization mechanism involving zwitterionic intermediate **4** (Scheme 7).[5a] Specifically, the reaction of (*E*)-**1a**-*c* ($R^2 = R^3 = Ph$), in which the alkyne sp-carbons were enriched with ^{13}C (15% and 85%, Scheme 8), was carried out in the presence of CuBr in toluene at 100 °C to afford (*E*)-**2a**-*c*, which possessed 15% ^{13}C at the nitrone carbon and 85% ^{13}C at the sp^2-carbon of the four-membered ring bound to the benzylidene group. This result indicates that our reaction does *not* proceed via cleavage of the carbon–carbon bond of the alkyne triple bond, but rather via cleavage of the carbon–oxygen bond.

The reaction of an equimolar mixture of (*E*)-**1a** and (*E*)-**1m** afforded only the normal products (*E*)-**2a** and (*E*)-**2m**; the formation of crossover products was not observed using LC-MS (Scheme 9). This result clearly indicates that the present reaction proceeds in an intramolecular manner.

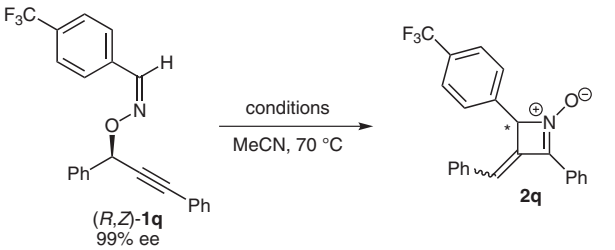
Scheme 8 ^{13}C-Labeling experiments



Scheme 9 Crossover experiments with (*E*)-**1a** and (*E*)-**1m**

To gain further insight into the reaction mechanism, we investigated the transfer of chirality during the Cu-catalyzed skeletal rearrangements (Scheme 10) using chiral substrates. Optically active (*R*,*E*)-**1q** was readily prepared via In-catalyzed asymmetric alkynylation,[8] then subjected to the rearrangement reaction under optimal reaction conditions (Table 3, entry 14). The resulting products (–,*E*)- and (+,*Z*)-**2q** were obtained in 77% ee and 80% ee, respectively, suggesting the effective transfer of chirality of the starting material. Furthermore, the choice of solvent significantly affected the chirality transfer – acetonitrile was the most effective – whereas less polar solvents such as CH_2Cl_2 and toluene decreased the enantioselectivity of the reaction (see Supporting Information). As a note, it was confirmed that racemization of (*R*,*E*)-**1q** and the isolated chiral products (–,*E*)-**2q** did not occur under the reaction conditions.

The reaction of the corresponding *Z*-isomer (*R*,*Z*)-**1q** (Scheme 11) afforded the same enantiomer (–)-**2q** as that of the reaction of (*R*,*E*)-**1q** (Scheme 10).



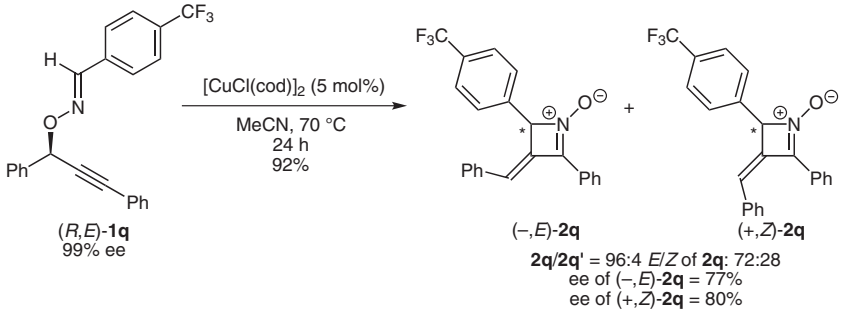
with [CuCl(cod)]$_2$ (5 mol%)	20 h	70%, **2q**/**2q**' = 95:5, *E*/*Z* of **2q**: 73:27 ee of (–,*E*)-**2q** = 87% ee of (+,*Z*)-**2q** = 89%
without Cu catalyst	110 h	90%, **2q**/**2q**' = 92:8, *E*/*Z* of **2q**: 76:24 ee of (–,*E*)-**2q** = 95% ee of (+,*Z*)-**2q** = 99%

Scheme 11 Cyclization of chiral *Z*-isomer (*R*,*Z*)-**1q**

Similarly, the chirality of substrates **1s**, **1aa**, and **1ab** were effectively maintained during the formation of products **2s**, **2aa**, and **2ab** as summarized in Table 6.

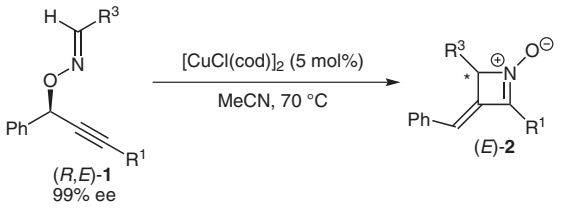
To determine the absolute configuration of the major product, the reaction of substrate (*R*,*E*)-**1z**, which has a 2-bromo-5-nitrophenyl group at the oxime moiety, was carried out under standard reaction conditions (Scheme 12). Although the *R*-configuration at the sp^3-carbon of major product (*E*)-**2z** was confirmed using X-ray crystallographic analysis (see Supporting Information); the yield, the ratio between **2z** and **2z′**, the *E*/*Z* ratio of **2z**, and the ee of (*E*)-**2z** were not determined because the crystallinity of **2z** was too high to conduct these analyses. And, the absolute configuration of the *Z*-product (*Z*)-**2z** cannot be determined at the present stage due to its poor crystallinity.

A plausible mechanism for the reaction of the *O*-propargylic aldoxime (*E*)-**1** is illustrated in Scheme 13. First, the π-acidic copper catalyst coordinates with the alkyne moiety of (*E*)-**1** to allow the nucleophilic attack by the oxime nitrogen atom onto the electrophilically-activated triple bond. The resulting five-membered cyclic intermediate **6** undergoes cleavage of the carbon–oxygen bond and elimination of the copper catalyst[9] to afford *N*-allenylnitrone



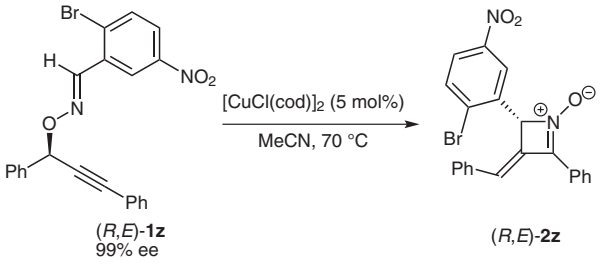
Scheme 10 Cyclization of chiral substrate (*R*,*E*)-**1q**

Table 6 Chirality Transfer for Copper-Catalyzed Reactions of **1s**, **1aa**, and **1ab**



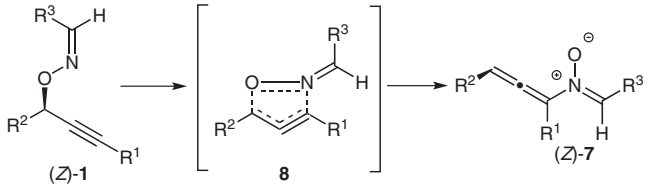
	1	R^1	R^3	Time (h)	2	Yield (%)[a]	*E*/*Z*[b]	ee (*E*/*Z*)[c]
1	**1s**	*n*-Pr	4-$F_3CC_6H_4$	36	**2s**	92[d]	72:28	78/78
2	**1aa**	Ph	4-BrC_6H_4	16	**2aa**	90[e]	72:28	81/85
3	**1ab**	Ph	4-MeC_6H_4	20	**2ab**	89[f]	–	76/75

[a] Isolated yield.
[b] The ratio was determined by ^{1}H NMR analysis.
[c] The value for ee was determined by HPLC analysis using a chiral stationary phase.
[d] The ratio of **2s**/**2s′** was 96:4.
[e] The ratio of **2aa**/**2aa′** was >99:1.
[f] The ratio of **2ab**/**2ab′** was 98:2

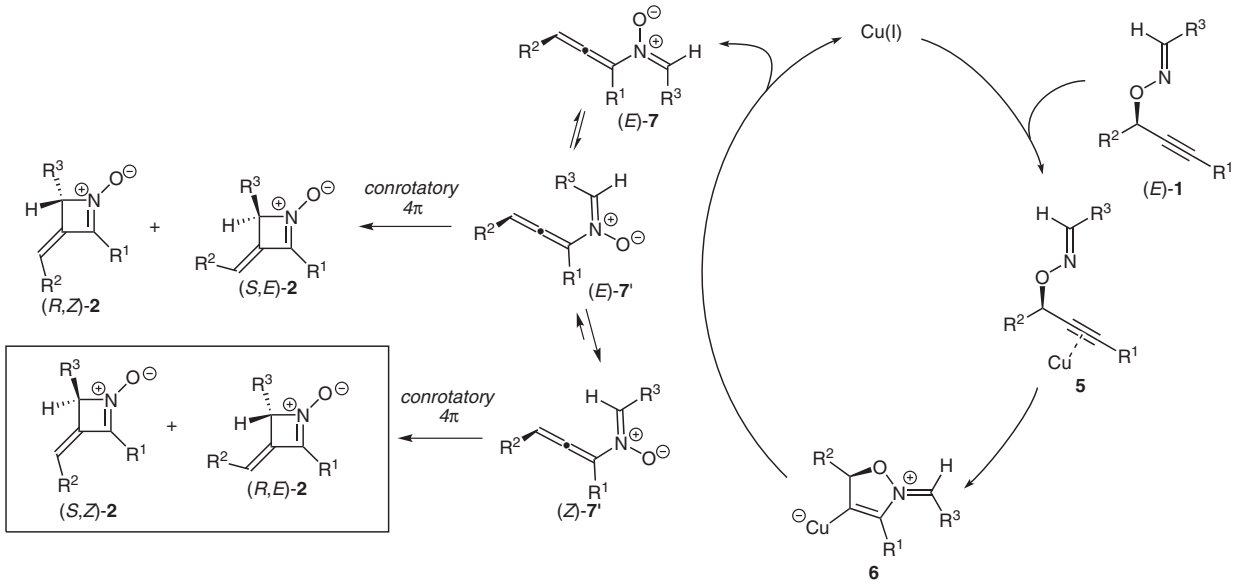


Scheme 12 Cyclization of (*R*,*E*)-**1z**

intermediate **7**, which then rotates to rotational conformer **7′** that undergoes cyclization to afford product **2**.[10] In the case of (*Z*)-**1**, the [2,3] rearrangement proceeds in a concerted manner to form *N*-allenylnitrone intermediate (*Z*)-**7**, without the aid of the copper catalyst, due to the lower steric repulsion between the alkyne substituent R^1 and the oxime moiety in the five-membered cyclic transition state **8** (Scheme 14).[4e] Should the cyclization of the chiral allene intermediate (*E*)-**7′** proceed via a conrotatory 4π-electrocyclization, the sp^3-carbon would adopt an *S*-configuration. However, the resulting *R*-configuration suggests that the aldonitrone moiety undergoes an *E*/*Z* isomerization to favor the more stable (*Z*)-**7′** prior to the thermal cyclization.[11] It should be noted that the reaction of ketoxime **1y** (Scheme 3) suggests that cyclization of (*E*)-**7′** can also take place. Accordingly, the lower level of the chirality transfer during the formation of (*E*)-**2q** can be attributed to the competitive 4π-cyclizations of the *E*- and *Z*-forms of *N*-allenylnitrone intermediate **7′**. This is in sharp contrast to the high level of chirality transfer for (*Z*)-**1q**, which proceeds directly via (*Z*)-*N*-allenylnitrone intermediate (*Z*)-**7′**. Moreover, isomerization from (*S*,*Z*)-**2** to (*S*,*E*)-**2** could result in low ee of the *E*-isomer (*E*)-**2** (Scheme 5). At the present stage, it is unclear whether the loss of ee takes place during the copper-catalyzed [2,3] rearrangement step from (*E*)-**1** to **7**.



Scheme 14 Thermal [2,3] rearrangement of *Z*-oxime (*Z*)-**1**



Scheme 13 A plausible mechanism for the formation of four-membered nitrones

In conclusion, we have developed novel synthetic methodology of preparing four-membered cyclic nitrones. In particular, nitrogen-containing chiral four-membered rings can be constructed with chirality transfer using readily accessible starting materials. For example, therefore, our methodology can be useful for the synthesis of azetidine derivatives. Further investigations on manipulation of the products are currently under way in our laboratory.

^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-α 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) spectrometer. Chemical shifts are reported in ppm relative to $CHCl_3$ (for ^{1}H, δ = 7.24), and $CDCl_3$ (for ^{13}C, δ = 77.00). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (standard abbreviations were used to indicate multiplicities), coupling constants (Hz), and integration. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. High-resolution mass spectra analysis was performed on a Bruker Daltonics APEX III FT-ICR-MS spectrometer at the Instrumental Analysis Center for Chemistry, Graduate School of Science, Tohoku University. X-ray crystallographic data was obtained by Rigaku/MSC Saturn Cu-CCD device at Graduate School of Science, Tohoku University. Flash column chromatography was performed with Kanto Chemical silica gel 60N (spherical, neutral, 40–50 μm). Analytical TLC was performed on Merck precoated TLC plates (silica gel 60 F_{254}). All reactions were carried out under argon atmosphere. Anhyd DMF, MeCN, 1,4-dioxane, THF, toluene, hexane (WAKO), and CuBr (WAKO, 99.9%) were purchased and used without further purification. CuCl (WAKO) was purified by recrystallization prior to use. $[CuCl(cod)]_2$ was prepared in accordance with the literature method.[12]

CuBr-Catalyzed Synthesis of (*E*)-3-Benzylidene-2,4-diphenyl-2,3-dihydroazete 1-Oxide [(*E*)-2a]; Typical Procedure

To a mixture of CuBr (5.72 mg, 0.040 mmol) and oxime (*E*)-**1a** (124.5 mg, 0.40 mmol) in a vial was added toluene (0.8 mL) under an argon atmosphere. After stirring at 100 °C for 24 h, the crude mixture was passed through a pad of silica gel with EtOAc (ca. 30 mL). Upon removal of the solvents in vacuo, the residue was purified using flash column chromatography with hexane–EtOAc (4:1) as the eluent to afford (*E*)-**2a** (121 mg, 96%) as a white solid; mp 189.8–190.6 °C.

IR (neat): 3052, 3028, 2964, 1954, 1893, 1685, 1576, 1545, 1488, 1409, 1311, 1224, 1207, 1193, 1152, 859 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.17 (s, 1 H), 6.94 (d, *J* =1.5 Hz, 1 H), 7.13–7.20 (m, 5 H), 7.34–7.38 (m, 3 H), 7.45–7.53 (m, 5 H), 8.18–8.20 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 86.30, 117.12, 126.46, 127.08, 127.62, 127.89, 128.57, 128.61, 128.81, 129.04, 129.78, 130.15, 130.21, 131.22, 134.95, 149.68.

HRMS (ESI): *m*/*z* calcd for $(C_{22}H_{17}NO + Na)^+$: 334.1202; found: 334.1201.

CuBr-Catalyzed Synthesis of (*E*)-3-Benzylidene-4-(2,6-dimethoxyphenyl)-2-[4-(trifluoromethyl)phenyl]-2,3-dihydroazete 1-Oxide [(*E*)-2p]; Typical Procedure

To a mixture of $[CuCl(cod)]_2$ (8.3 mg, 0.020 mmol) and oxime (*E*)-**1p** (175.8 mg, 0.40 mmol) in a vial was added MeCN (0.8 mL) under an argon atmosphere. After stirring at 70 °C for 14 h, the crude mixture was passed through a pad of silica gel with EtOAc (ca. 30 mL). Upon removal of the solvents in vacuo, the residue was purified using flash column chromatography with hexane–EtOAc (4:1) as the eluent to afford a 95:5 mixture of (*E*)-**2p** and (*Z*)-**2p** (161 mg, 91%). The *E*/*Z* (95:5) isomers were separated using flash silica gel column chromatography.

(*E*)-2p

White solid; mp 75.5–77.6 °C.

IR (neat): 3057, 3023, 3002, 2965, 2938, 2839, 1691, 1599, 1586, 1547, 1473, 1446, 1432, 1402, 1322, 1257, 1165, 106, 1065, 1019, 859, 818 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.88 (s, 6 H), 6.16 (s, 1 H), 6.35 (s, 1 H), 6.63 (d, *J* = 8.5 Hz, 2 H), 7.08–7.18 (m, 5 H), 7.41 (d, *J* = 8.5 Hz, 1 H), 7.64 (d, *J* = 8.0 Hz, 2 H), 7.71 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 56.00, 84.66, 103.22, 103.87, 104.11, 116.16, 120.59, 122.77, 124.93, 125.85, 125.88, 125.91, 125.94, 127.09, 127.30, 127.42, 128.50, 129.11, 131.06, 131.32, 131.83, 131.97, 132.83, 135.05, 136.02, 148.84, 159.36.

HRMS (ESI): *m*/*z* calcd for $(C_{25}H_{20}F_3NO_3 + Na)^+$: 462.1287; found: 462.1284.

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

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