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Regioselective Transformation of *O*-Propargylic Arylaldoximes to Four-Membered Cyclic Nitrones by Copper-Catalyzed Skeletal Rearrangement

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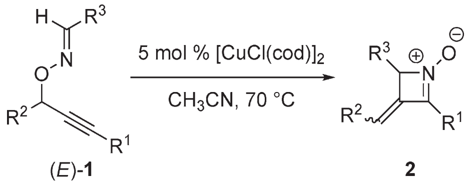
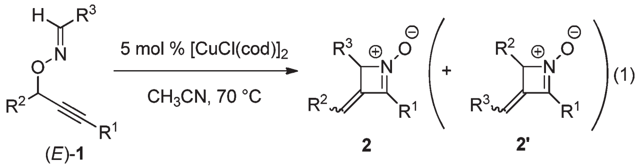
ABSTRACT



(*E*)-*O*-Propargylic arylaldoximes were regioselectively converted, in the presence of copper catalysts, into their corresponding four-membered cyclic nitrones in good to excellent yields. The reactions proceeded via a tandem [2,3]-rearrangement and 4π-electrocyclization of the *N*-allenylnitrone intermediate and involved cleavage of the carbon–oxygen bond.

Metal-catalyzed skeletal rearrangements have been utilized in elegant transformations, often via unique reaction mechanisms, in the construction of complex molecules. Since the pioneering works by Trost,[1] such skeletal rearrangements have mainly focused on 1,*n*-enynes[2] or propargylic esters[3] as substrates. Recently, however, we have demonstrated that *O*-propargylic oximes, in the presence of π-acidic metal catalysts, can act as attractive substrates for skeletal rearrangements.[4] In particular, we reported that the copper-catalyzed skeletal rearrangement of *O*-propargylic arylaldoximes **1** afforded the corresponding four-membered cyclic nitrones **2** in good yields.[5] However, there was an obvious drawback in the regioselectivity, when **1** has different substituents at the propargylic position and the oxime moiety ($R^2 \neq R^3$) (eq 1). Herein, we report on the copper-catalyzed skeletal rearrangement of (*E*)-**1** that produced **2** with excellent regioselectivities by using $[CuCl(cod)]_2$ as catalysts under mild reaction conditions (eq 1).[6] Moreover, mechanistic studies revealed that the present reaction proceeds via a tandem [2,3]-rearrangement and 4π-electrocyclization.



Previously, (*E*)-**1a** was transformed in the presence of copper bromide (10 mol %) in toluene at 100 °C for 42 h to afford a 68:32 mixture of the corresponding cyclic nitrone **2a** and its regioisomer **2a′** in 96% isolated yield (Table 1,

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(1) For pioneering works: (a) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636. (b) Trost, B. M.; Trost, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 1850.

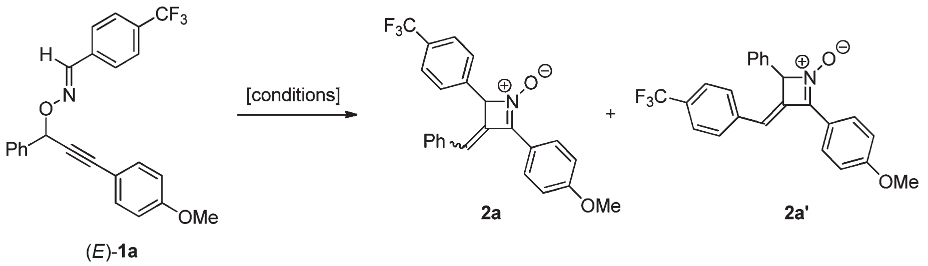
(2) For selected reviews: (a) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (b) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. (c) Añorbe, L.; Domínguez, G.; Pérez-Castells, J. *Chem.—Eur. J.* **2004**, *10*, 4938. (d) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. (e) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (f) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (g) Tobisu, M.; Chatani, N. *Chem. Soc. Rev.* **2008**, *37*, 300.

(3) For selected reviews: (a) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750. (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (c) Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 718. (d) Wang, S.; Zhang, G.; Zhang, L. *Synlett* **2009**, 692.

(4) (a) Nakamura, I.; Zhang, D.; Terada, M. *J. Am. Chem. Soc.* **2010**, *132*, 7884. (b) Nakamura, I.; Okamoto, M.; Terada, M. *Org. Lett.* **2010**, *12*, 2453. (c) Nakamura, I.; Zhang, D.; Terada, M. *J. Am. Chem. Soc.* **2011**, *133*, 6862.

10.1021/ol2012583

Table 1. Optimization of the Reaction Conditions



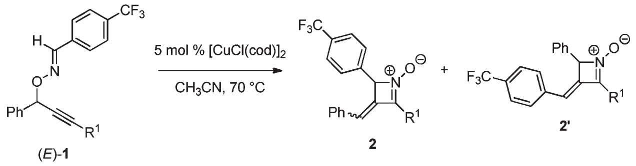
entry	catalyst (mol %)	solvent	temp, °C	time, h	yield, %[a]	**2a**:**2a′**	*E*:*Z* of **2a**
1	CuCl (10)	toluene	100	24	94	70:30	>99:1
2	CuBr (10)	toluene	100	42	96	68:32	>99:1
3	CuI (10)	toluene	100	48	18	72:28	>99:1
4	CuOAc (10)	toluene	100	27	91	85:15	84:16
5	[CuCl(cod)]$_2$ (5)	toluene	100	7	quant	73:27	90:10
6	[CuCl(cod)]$_2$ (5)	CH_2Cl_2	100	4.5	quant	81:19	78:22
7	[CuCl(cod)]$_2$ (5)	1,4-dioxane	100	7	46	82:18	84:16
8	[CuCl(cod)]$_2$ (5)	CH_3CN	100	3	(90)	87:13	80:20
9	[CuCl(cod)]$_2$ (5)	CH_3CN	70	14	99(92)	98:2	74:26
10	none	CH_3CN	100	24	0[b]	-	-

[a] Combined yields of **2a** and **2a′**. The yield and ratio were determined using ^{1}H NMR with CH_2Br_2 as an internal standard. Isolated yield in parentheses. [b] 98% of (*E*)-**1a** was recovered.

entry 2).[5] Whereas the reactions were effectively catalyzed by either copper chloride or bromide, the use of copper iodide exhibited significantly lower catalytic activity (entries 1−3). Among the copper catalysts tested, [CuCl(cod)]$_2$ gave the highest activities (entries 5−9). Regioselectivity of the present reaction was significantly affected by the solvent (entries 5−8). In particular, the use of acetonitrile gave **2a** with high regioselectivity and moderate *E*/*Z* stereoselectivity (entry 8). Moreover, excellent regioselectivity was attained by conducting the reaction at 70 °C (entry 9). In the absence of the copper catalyst, however, the reaction did not proceed, even at 100 °C (entry 10).

Subsequently, the optimal conditions (Table 1, entry 9) were employed for other (*E*)-**1** substrates. Substrates having an electron-rich aromatic ring at the alkyne terminus [(*E*)-**1a**, **-1b**, **-1c**] afforded products with high regioselectivities (Table 2, entries 1−3, respectively)—in particular, bulky substituents at R^1 resulted in high stereoselectivity of the (*E*)-isomer at the olefinic moiety (entries 2 and 3). In contrast, substrate (*E*)-**1e**, which possesses an electron-deficient *p*-(trifluoromethyl)phenyl group, resulted in products with low regioselectivity (entry 5). Substrates having an alkyl group at the alkyne terminus [(*E*)-**1f** and **-1g**] afforded nitrones **2f** and **2g**, respectively, in excellent yields and with high regioselectivities (entries 6 and 7, respectively).

Table 2. Copper-Catalyzed Reactions of **1a**−**1g** [a]



	1	R^1	time	2	yield, % [b]	2:2′	*E*:*Z* of 2
1	**1a**	*p*-$MeOC_6H_4$	16 h	**2a**	92	98:2	74:26
2	**1b**	2-$MeOC_{10}H_6$	4 days	**2b**	82	95:5	97:3
3	**1c**	2,6-$(MeO)_2C_6H_3$	4 days	**2c**	91	99:1	95:5
4	**1d**	Ph	24 h	**2d**	86	94:6	73:27
5	**1e**	*p*-$F_3CC_6H_4$	48 h	**2e**	89	91:9	74:26
6	**1f**	*n*-Pr	36 h	**2f**	91	97:3	73:27
7	**1g**	Cy	7 days	**2g**	95	93:7	83:17

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

Substrates with an alkyl group at the propargylic position (R^2) required an elevated reaction temperature (100 °C) to afford the desired products in good yields (Table 3, entries 1 and 2). As a note, the reaction of (*E*)-**1k** having a *p*-anisyl group on its oxime moiety did not afford the desired product due to the decomposition of the

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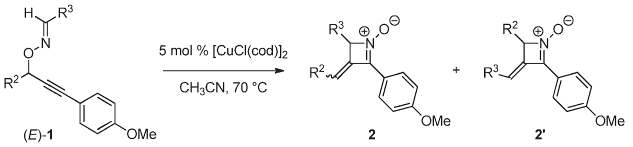
(5) We previously reported the structure of the product as 4-arylidene-*β*-lactam. However, thorough analysis of X-ray crystallographic data has indicated that the structure of cyclic nitrone was more valid than that of *β*-lactam. Moreover, vibrational analysis by DFT calculations suggests the cyclic nitrone structure (see Supporting Information). (a) Nakamura, I.; Araki, T.; Terada, M. *J. Am. Chem. Soc.* **2009**, *131*, 2804 (withdrawn). (b) Nakamura, I.; Araki, T.; Terada, M. *J. Am. Chem. Soc.* **2011**, *133*, 6861.

(6) Four-membered cyclic nitrone: (a) Pennings, M. L. M.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J. *J. Am. Chem. Soc.* **1980**, *102*, 7570. (b) Pennings, M. L. M.; Reinhoudt, D. N. *J. Org. Chem.* **1983**, *48*, 4043. (c) Verboom, W.; van Eijk, P. J. S. S.; Conti, P. G. M.; Reinhoudt, D. N. *Tetrahedron* **1989**, *45*, 3131.

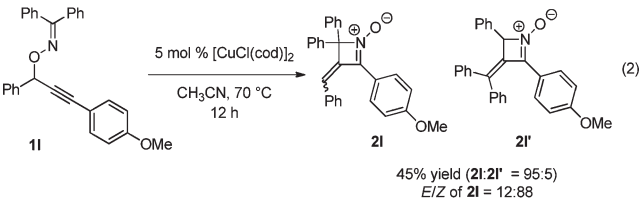
starting compound under the reaction conditions (entry 4). The reaction of ketimine **1l** afforded the product in a moderate yield (eq 2).

Table 3. Copper-Catalyzed Reactions of **1h**–**1k** [a]



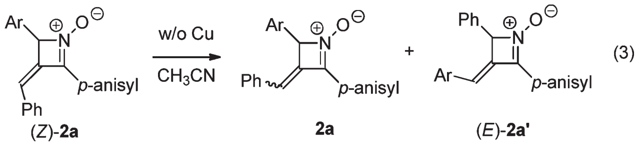
	1	R^2	R^3	time	2	yield, %[b]	2:2′	E:Z of 2
1[c]	**1h**	*n*-Pr	*p*-$F_3CC_6H_4$	24 h	**2h**	77	98:2	73:27
2[c]	**1i**	*i*-Pr	*p*-$F_3CC_6H_4$	25 h	**2i**	71	95:5	74:26
3	**1j**	Ph	2-naphthyl	18 h	**2j**	88	97:3	74:26
4	**1k**	Ph	*p*-anisyl	16 h	-	nd	-	-

[a] The reaction of (*E*)-**1** (0.4 mmol) was conducted in the presence of 5 mol % of [CuCl(cod)]$_2$ in acetonitrile (0.8 mL) at 70 °C. [b] Combined yield of **2** and **2′**. The ratio was determined using ^{1}H NMR. [c] At 100 °C.



45% yield (**2l**:**2l'** = 95:5)
E/*Z* of **2l** = 12:88

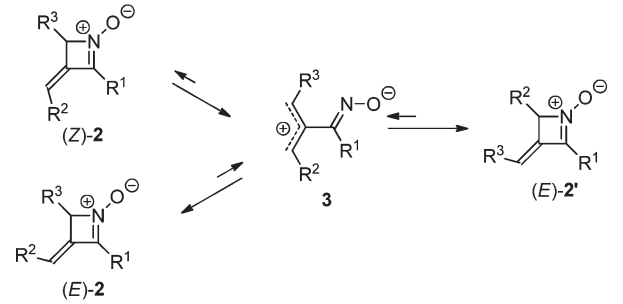
Next, isomerization experiments were carried out to gain insight into the mechanism of the reactions. Product (*Z*)-**2a**, albeit a minor product, was successfully converted to isomers (*E*)-**2a** and (*E*)-**2a′**, in the absence of copper catalysts, at 100 °C. However, the conversion did not occur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



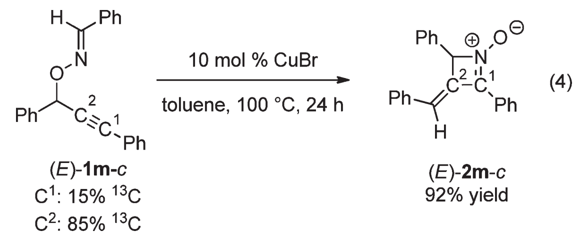
Ar: *p*-F_3C-C_6H_4

At 100 °C, 12 h 83% yield, **2a**:**2a'** = 41:59, E/Z of **2a** = 93:7
At 70 °C, 14 h 92% yield, **2a**:**2a'** = 92:8, E/Z of **2a** = 20:80

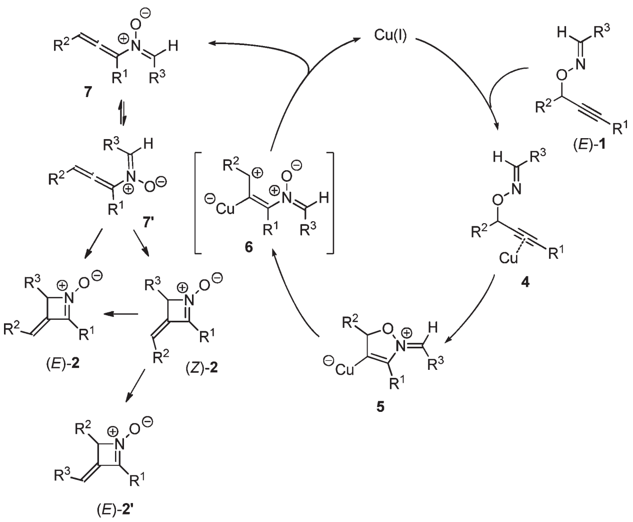
Scheme 1. Isomerization of (*Z*)-**2** through Zwitterionic Intermediate **3**



Moreover, previous ^{13}C-labeling experiments (eq 4) are in agreement with the isomerization mechanism involving zwitterionic intermediate **3** (Scheme 1).[5a] That is to say, the reaction of (*E*)-**1m-*c*** ($R^2 = R^3 = $ Ph), in which the alkyne sp-carbons were enriched with ^{13}C (15% and 85%, see eq 4), with a catalytic amount of copper bromide in toluene at 100 °C afforded (*E*)-**2m-*c***, which possessed ^{13}C content of 15% at the nitrone carbon and 85% at the sp^2-carbon within the four-membered ring bound to the benzylidene group. This result indicates that the carbon–carbon bond of the alkyne triple bond does not cleave during the reaction. Apparently, the present reaction proceeds via cleavage of the carbon–oxygen bond.



Scheme 2. Plausible Mechanism



A plausible mechanism for the reaction of (*E*)-**1** is illustrated in Scheme 2. First, the π-acidic copper catalyst coordinates with the alkyne moiety of (*E*)-**1**. Next, nucleophilic attack by the oxime nitrogen atom onto the electrophilically activated triple bond leads to the five-membered cyclic intermediate **5**. Then, *N*-allenylnitrone intermediate **7** forms either via stepwise process through cleavage of the carbon–oxygen bond and subsequent elimination of the copper catalyst (**5** → **6** → **7**) or via direct process via fragmentation of **5** through a concerted pathway.[8] The key intermediate **7** rotates into its rotational conformer (**7′**) and then undergoes a 4π-electrocyclization to afford product **2**.[9] Further mechanistic studies are underway in our laboratory.

In conclusion, we have developed a novel and efficient synthetic method for the construction of highly strained four-membered cyclic nitrones from readily available *O*-propargylic arylaldoximes. Further transformation of the present products is now being studied in our laboratory.

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Supporting Information Available. Experimental procedures and characterization of **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The reaction of (*E*)-**2a** at 100 °C for 12 h afforded a > 97:3 mixture of (*E*)-**2a** and (*E*)-**2a′**.

(8) Pd(II)-catalyzed [2,3] rearrangement of *O*-allyl oximes: Grigg, R.; Markandu, J. *Tetrahedron Lett.* **1991**, *32*, 279.

(9) 4π-Azabutadiene electrocyclization: (a) Bongini, A.; Panunzio, M.; Tamanini, E.; Martelli, G.; Vicennati, P.; Monari, M. *Tetrahedron: Asymmetry* **2003**, *14*, 993. (b) Liang, Y.; Jiao, L.; Zhang, S.; Xu, J. *J. Org. Chem.* **2005**, *70*, 334.