Heterocycles

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Oxazepine Synthesis by Copper-Catalyzed Intermolecular Cascade Reactions between O-Propargylic Oximes and Dipolarophiles**

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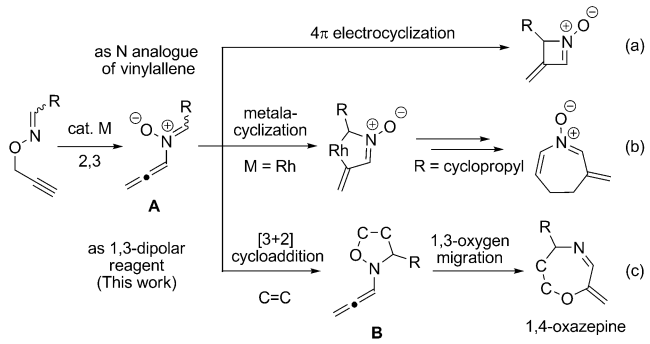
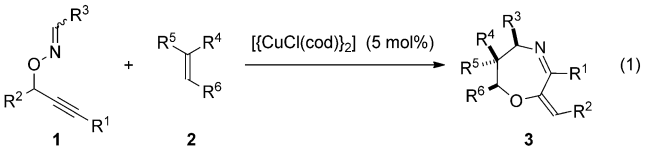
π-Acidic metal-catalyzed rearrangement reactions have been often utilized in cascade reactions because the transformation efficiently generates reactive intermediates, which are generally hard to pre-prepare by conventional organic synthesis, under mild reaction conditions with high functional-group tolerance.[1–3] In particular, the cascade reaction involving an intermolecular process between a reactive intermediate and an external reagent is an attractive and elegant protocol for the construction of densely functionalized molecular skeletons in a single operation. Although the reactivities of the metal carbenoid intermediates, which are generated by alkyne π activation, typically drive the intermolecular process,[4] cycloadditions have also been utilized as a viable alternative in an intermolecular fashion.[5] Recently, we have developed π-acidic metal-catalyzed intramolecular reactions of O-propargylic oximes proceeding through a 2,3-rearrangement to form the corresponding N-allenylnitrone **A** (Scheme 1). The key intermediate **A** acts as a nitrogen analogue of vinylallene which can undergo electrocyclization and metalacyclization (Scheme 1a and b). Meanwhile, we expected that the proposed intermediate **A** would possess alternative reactivity as the 1,3-dipolar reagent. In other words, the reaction step would involve an intermolecular [3+2] cycloaddition with a dipolarophile (C=C; Scheme 1c).[7,8] Moreover, we envisioned that the resulting N-allenylisoxazolidine **B** would undergo a subsequent rearrangement, specifically 1,3-oxygen migration from the nitrogen atom to the allene center carbon atom,[9] to afford the 1,4-oxazepine skeleton which is often found in biologically active molecules.[10] Herein, we report on the copper-catalyzed reactions between the O-propargylic oximes **1** and dipolarophiles **2**, such as maleimides and fumaric acid esters, in affording the corresponding oxazepine derivatives **3** by 2,3-rearrangement, [3+2] cycloaddition, and 1,3-oxygen migration [Eq. (1)].



Scheme 1. Transformation of the N-allenylnitrone intermediate **A**. a) 4π-electrocyclization, b) metalacyclization, and c) [3+2] dipolar cycloaddition (this work).



Initially, the reaction between the formaldoxime **1a** and *N*-methylmaleimide (**2a**; 1.5 equiv) was carried out in the presence of 5 mol% of [{CuCl(cod)}$_2$] (cod = 1,5-cyclooctadiene) in 1,4-dioxane at 30 °C to afford **3a** in 67% yield upon isolation (Table 1, entry 1).[11] Whereas [{CuCl(cod)}$_2$] and CuCl were effective as catalysts, the use of CuBr, $CuCl_2$, and $Cu(OAc)_2$ resulted in lower yields (see the Supporting Information). Other metal salts such as $PtCl_2$ and AuCl, were not effective in catalyzing the reaction. In terms of solvents, the use of 1,4-dioxane, toluene, THF, and CH_2Cl_2 gave favorable results, while EtOAc and acetonitrile resulted in lower yields (see the Supporting Information). In the absence of copper catalysts, however, the reaction did not proceed; **1a** was quantitatively recovered.[12] Then, the reactivity of the dipolarophiles **2** was investigated as summarized in Table 1. Among the maleimides examined, *N*-phenylmaleimide (**2c**) gave the highest yield of **3c** (entry 3). As a note, a *tert*-butyl group on the nitrogen atom was tolerated (entry 2), and the nonprotected maleimide **2f** resulted in a sluggish reaction (entry 6). The reaction of **1a** with fumaric acid esters **2g** and **2h** using acetonitrile as the solvent afforded the desired products **3g** and **3h**, respectively.[13] The *E* configuration of the dipolarophile was ste-

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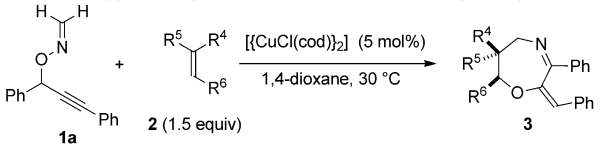
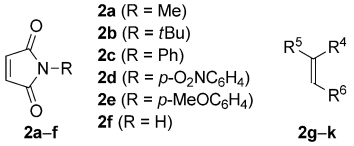
Table 1: Copper-catalyzed reaction of **1a** and the dipolarophiles **2a–k**.[a]





	R^4	R^5	R^6
2g	H	CO_2Me	CO_2Me
2h	H	CO_2iPr	CO_2iPr
2i	CO_2Me	H	CO_2Me
2j	H	H	CO_2Me
2k	H	H	$CONMe_2$

Entry	2	t [h]	3	Yield [%][b]
1	**2a**	20	**3a**	67
2	**2b**	12	**3b**	61
3	**2c**	16	**3c**	77
4	**2d**	12	**3d**	55
5	**2e**	24	**3e**	67
6	**2f**	36	**3f**	39
7[c,d]	**2g**[e]	6	**3g**	63
8[c,d]	**2h**[e]	6	**3h**	59
9[c,d]	**2i**[f]	6	**3i**	25
10[c]	**2j**[g]	18	**3j**	40
11[c]	**2k**[e]	84	**3k**	28

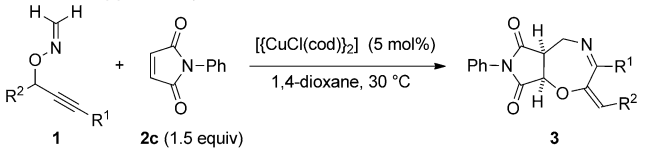
[a] The reactions of **1a** (0.2 mmol) and **2** (0.3 mmol) were carried out in the presence of [{CuCl(cod)}2] (5 mol%) in 1,4-dioxane (0.2 mL) at 30°C. [b] Yield of isolated product. [c] Acetonitrile was used as solvent. [d] At 50°C. [e] Used 3 equivalents of **2**. [f] Used 7 equivalents of **2**. [g] Used 5 equivalents of **2**.

reospecifically transferred to the *anti* stereochemistry between two ester groups (R^5 and R^6) of the product (entries 7 and 8).[11] Methyl acrylate (**2j**) was also employed as a dipolarophile, thus producing **3j** in a regioselective manner, albeit in moderate chemical yield (entry 10). Other dipolarophiles, such as maleic anhydride, vinyl phenyl sulfone, and naphthoquinone, did not give the desired products; a mixture of unidentified byproducts was obtained.

Various O-propargylic formaldoximes (**1a–i**) were employed for the reaction with **2c** (Table 2). The substrates **1b** and **1c**, both with an aryl substituent at the alkyne terminus, were efficiently converted into the corresponding products in good yields (entries 1 and 2). Although the reaction of **1e** (R^1 = cyclohexyl group, entry 4) was highly effective, the reaction of **1d** (R^1 = *n*-propyl group, entry 3) resulted in a low yield of the product **3n** along with the formation of unidentified byproducts. The reactions of **1f** and **1g**, both possessing an aromatic group at the propargyl position, afforded the corresponding products in good yields (entries 5 and 6). The reactions of **1h** and **1i**, both having an alkyl group as R^2, produced the desired products in acceptable yields with prolonged reaction times (entries 7 and 8, respectively). It should be noted that the configuration of exocyclic double bond of the products **3a–s** was *E*, and the corresponding *Z* isomer was not detected.

For the reaction between the *Z* isomer of the arylaldoxime, (*Z*)-**1j**, and **2c**, high diastereoselectivity was observed when the reaction was carried out in acetonitrile or 1,4-dioxane at 50°C (Table 3, entries 1 and 2).[14,15] In contrast, for

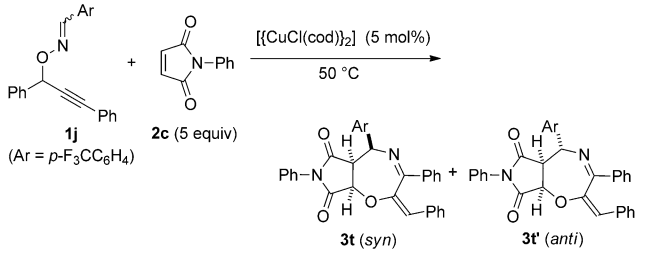
Table 2: Copper-catalyzed reaction of the formaldoximes **1b–i** and **2c**.[a]



Entry	1	R^1	R^2	t [h]	3	Yield [%][b]
1	**1b**	*p*-$F_3CC_6H_4$	Ph	15	**3l**	76
2	**1c**	*p*-$MeOC_6H_4$	Ph	12	**3m**	64
3	**1d**	*n*Pr	Ph	12	**3n**	41
4	**1e**	Cy	Ph	10	**3o**	91
5	**1f**	Ph	*p*-$MeOC_6H_4$	14	**3p**	75
6[c]	**1g**	Ph	*p*-$F_3CC_6H_4$	12	**3q**	84
7[d,e]	**1h**	Ph	*n*Pr	22	**3r**	62
8	**1i**	Ph	Me_3SiCH_2	48	**3s**	55

[a] The reactions of **1** (0.2 mmol) and **2c** (0.3 mmol) were carried out in the presence of [{CuCl(cod)}2] (5 mol%) in 1,4-dioxane (0.2 mL) at 30°C. [b] Yield of isolated product. [c] Used 3 equivalents (0.6 mmol) of **2c**. [d] Used 5 equivalents (1.0 mmol) of **2c**. [e] Used 3 mol% of [{CuCl(cod)}2].

Table 3: Copper-catalyzed reaction of arylaldoxime **1j** and **2c**.[a]



Entry	E/Z[b]	Solvent	t [h]	Yield [%][c]	3t/3t'[d]
1	*Z*	CH_3CN	2	71	>99:1
2	*Z*[e]	1,4-dioxane	2.5	76	93:7
3[f,g]	*Z*	1,4-dioxane	120	0[h]	–
4	*E*[i]	CH_3CN	72	63	>99:1
5	*E*	1,4-dioxane	24	67	69:31
6	*E*	toluene	24	55	51:49

[a] The reactions of **1j** (0.2 mmol) and **2c** (1.0 mmol) were carried out in the presence of [{CuCl(cod)}2] (5 mol%) in solvent (0.2 mL) at 50°C. [b] *E*/*Z* stereochemistry at the oxime moiety of **1j**. [c] Combined yields of **3t** and **3t'**. [d] The ratio was determined by ^{1}H NMR spectroscopy. [e] Chiral substrate (*R*,*Z*)-**1j** (99% *ee*) was used (**3t**: 2% *ee*, **3t'**: 30% *ee*). [f] The reaction was carried out in the absence of copper catalysts. [g] At 70°C. [h] Obtained 28% of (*E*)-**1j**. [i] Chiral substrate (*R*,*E*)-**1j** (99% *ee*) was used (**3t**: <5% *ee*).

the reaction involving the *E* isomer, (*E*)-**1j**, and **2c**, the diastereoselectivity was significantly affected by the choice of the solvent (entries 4–6). Polar solvents such as acetonitrile afforded the *syn*-product **3t** with high diastereoselectivity (entry 4), whereas less polar solvents such as 1,4-dioxane and toluene resulted in low diastereoselectivities (entries 5 and 6). It should be noted that the reaction of (*Z*)-**1j** with **2c** in the absence of copper catalysts afforded neither the oxazepine **3t**/**3t'** nor four-membered cyclic nitrones derived from intramolecular reaction of (*Z*)-**1j** (entry 3).[6b]

Based on these experiments, a plausible mechanism for the present reaction of **1** and **2c** is illustrated in Scheme 2.

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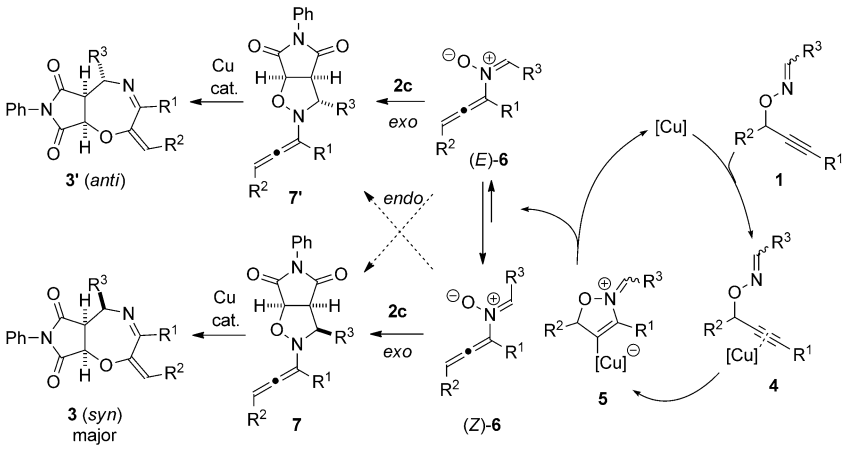

Scheme 2. A plausible mechanism.

First, the carbon–carbon triple bond of the O-propargylic oximes **1** is coordinated by the π-acidic copper catalyst leading to the π-complex **4**. Nucleophilic attack of the oxime nitrogen atom onto the electrophilically activated alkyne moiety by 5-*endo*-dig cyclization gives the vinyl-copper intermediate **5**. Cleavage of the carbon–oxygen bond and subsequent elimination of the copper catalyst leads to the N-allenylnitrone intermediate **6**. Next, the [3+2] cycloaddition of the nitrone moiety of **6** with the maleimides **2c** leads to either *N*-allenylisoxazolidine **7** or **7′**, and subsequent 1,3-oxygen migration from the nitrogen atom to the allene center carbon atom to give either **3** or **3′**, respectively.[16,17] The selective formation of the *syn* diastereomer **3** from (*Z*)-**1j**, which directly generates the thermodynamically more stable (*Z*)-**6**, indicates that the [3+2] cycloaddition proceeds primarily in an *exo* manner. This high diastereoselectivity probably results because steric repulsion between the allene moiety of **6** and the approaching dipolarophile interferes with the *endo* [3+2] cycloaddition.[18] The diastereoselective reaction of (*E*)-**1** required the use of acetonitrile, probably because the *E*/*Z* isomerization at the nitrone moiety of the N-allenylnitrone intermediate **6** is facilitated by polar solvents (Table 3, entries 4–6). Notably, the N-allenylnitrone shows the reactivity of a dipolar reagent for [3+2] cycloaddition, in contrast to N-vinylnitrone, which acts as an azadiene for a [4+2] cycloaddition according to the report from Denmark and Montgomery.[17] The reaction between (*Z*)-**1j** and **2c** in the absence of copper catalysts gave neither the desired product **3t** nor the four-membered cyclic nitrone (Table 3, entry 3), despite our knowledge that both 2,3-rearrangement of (*Z*)-**1j** and subsequent [3+2] cycloaddition, which is faster than 4π electrocyclization, proceed even in the absence of a copper catalyst.[6d] This result implies that the 1,3-oxygen migration process from **7** to **3** is also promoted by the copper catalyst, although the mechanism is not clear at the present stage.

In conclusion, we have developed an efficient method for the synthesis of multisubstituted oxazepine derivates in a single operation. Because the oxazepine backbone is often present in biologically active molecules, the present methodology can prove to be useful for the synthesis of such compounds.[10]

Experimental Section

1a (47.1 mg, 0.2 mmol) was added to a mixture of [{CuCl(cod)}$_2$] (4.1 mg, 0.01 mmol) and *N*-phenylmaleimide (**2c**; 52.0 mg, 0.3 mmol) in 1,4-dioxane (0.2 mL) in a pressure vial was added. After stirring the mixture at 30 °C for 16 h, the reaction mixture was passed through a short pad of silica gel with EtOAc (50 mL). After removing the solvents in vacuo, the crude reaction mixture was purified using flash column chromatography with *n*-hexane/EtOAc (5:1) as eluents to afford pure **3c** (62.9 mg, 77 %).

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Keywords: copper · cycloaddition · heterocycles · rearrangement · synthetic methods

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[11] CCDC 910036 (**3a**) and 928256 (**3g**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] The reaction of **1g** without the dipolarophile **2** in the presence of 5 mol% of [{CuCl(cod)}$_2$] at 30 °C in dioxane resulted in the decomposition of **1g**. The corresponding four-membered cyclic nitrone (Ref. [6b]) was not obtained presumably because of the instability of the nitrone derived from formaldoxime.

[13] The reaction of **1a** and **2g** (3 equiv) in 1,4-dioxane at 50 °C afforded **3g** in 52% yield.

[14] The relative stereochemistry of **3** and **3′** was determined based on X-ray crystallographic analysis of **3u** (CCDC 910037), which was obtained from the reaction of **1k** (R^1 = *p*-anisyl, R^2 = Ph, R^3 = *p*-$F_3CC_6H_4$) and **2a**, and comparison of the ^{1}H NMR spectra. See the Supporting Information.

[15] The reaction of four-membered cyclic nitrone, which is derived from **1j**, and **3c** under the reaction conditions did not give the product **3t**.

[16] Neither the N-allenylnitrone **6** nor the N-allenylisoxazolidines **7** or **7′** were observed.

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[18] Indeed, the reaction between the chiral oxime (*R*,*Z*)-**1j** (99% *ee*) and **2c** afforded **3t** (2% *ee*) and **3t′** (30% *ee*), thus indicating that the chirality of the allene moiety does not affect the [3+2] cycloaddition step (Table 3, footnote [e]). The poor chirality transfer in the reaction of (*R*,*Z*)-**1j** and **2c** (Scheme 2) can be attributed to the *exo* [3+2] cycloaddition step, in which the dipolarophile **2** approaches the distal side of the chiral allene moiety of N-allenylnitrone (*Z*)-**6**. Accordingly, the minor product **3t′**, which formed through *endo* [3+2] cycloaddition, exhibited higher enantiomeric excess (30% *ee*) than that of **3t**.

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