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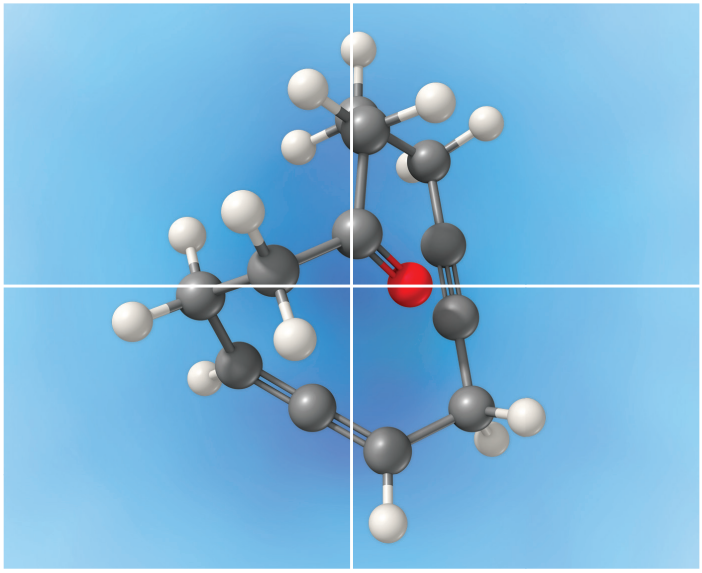

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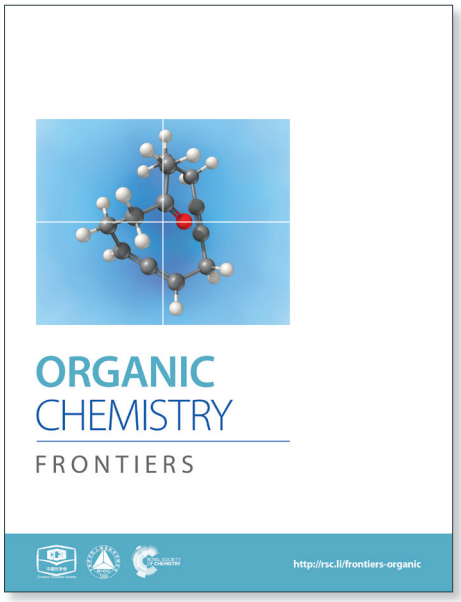

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N-Allenylnitrone Acts as 2-Azadiene in the Cu-Catalyzed Cascade Reaction of *O*-Propargylic Oximes with Azodicarboxylates

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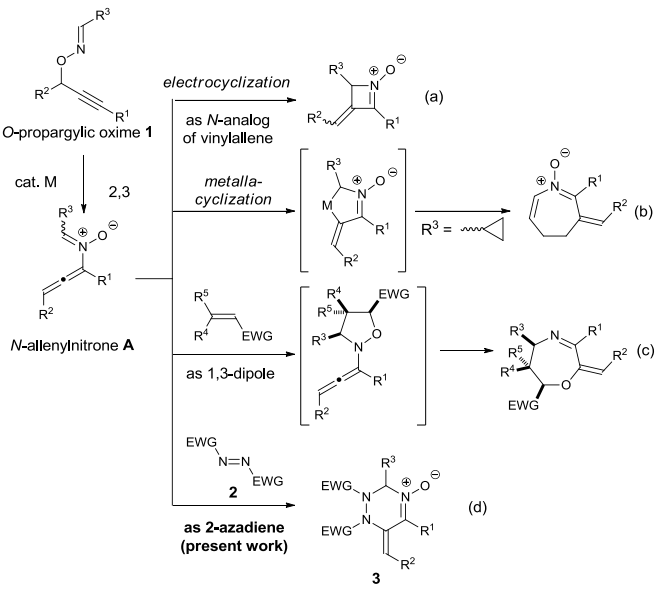
The reaction of *O*-propargylic oximes with azodicarboxylates efficiently afforded 1,2,4-triazine oxides in good yields. The key intermediate, *N*-allenylnitrone, acted as 2-azadiene, undergoing stepwise [4+2] cycloaddition.

π-Acidic metal-catalyzed rearrangements have been efficiently utilized for cascade reactions because the transformations proceed under mild reaction conditions and tolerate a wide variety of functional groups to afford reactive intermediates that are inaccessible by conventional organic synthesis.[1,2] The key intermediates often feature multiple reactivities as seen in homoallyl cation–cyclopropylcarbenoid–cyclobutyl cation in the enyne cycloisomerization[3] and allene–enol–vinylcarbenoid in the catalytic skeletal rearrangement of propargylic esters.[4] Those multiple reactivities are typically controlled by the sophisticated design of the starting materials or the appropriate choice of reagents for the synthesis of diverse organic molecules. Thus, the discovery of new reaction modes of the reactive intermediates is a fundamental challenge in the development of catalytic cascade reactions. We have recently demonstrated that *N*-allenylnitrone intermediate **A**, which is generated from *O*-propargylic oxime **1** via a metal-catalyzed 2,3-rearrangement, acts as a nitrogen analog of vinylallene and undergoes further transformations, such as thermal electrocyclization (type a)[5] and aza-metallacyclic formation[6] (type b). Moreover, we have disclosed that *N*-allenylnitrone intermediate **A** shows a second reactivity as a 1,3-dipolar reagent in the cascade reaction with dipolarophiles, such as electron-deficient olefins and isocyanates (type c).[7] However, Denmark's pioneering report[8a] demonstrating the [4+2] cycloaddition of *N*-vinylnitrone species inspired us to come up with the idea that key intermediate **A** possesses a third reactivity as "2-azadiene" (type d). Specifically, we envisioned that the reaction of *N*-allenylnitrone **A** with the diazene (RN=NR) would proceed via the [4+2] cycloaddition[9] preferentially, rather than the [3+2] dipolar cycloaddition,[10] because the latter reaction would proceed through unfavorable transition state due to electrostatic repulsion between lone pairs on the nitrone O atom and the diazene N atom, forming of a weak N-O bond.[11] Moreover, since the expected [4+2] cycloadducts, 1,2,4-triazines have been frequently utilized in pharmaceutical and agrochemical fields,[12] the envisioned transformation appears promising from the synthetic viewpoint. Herein, we report that the copper-catalyzed intermolecular reaction of *O*-propargylic oximes **1** with azodicarboxylates **2** afforded corresponding 1,2,3,6-tetrahydro-1,2,4-triazine oxides **3** in good to high yields.

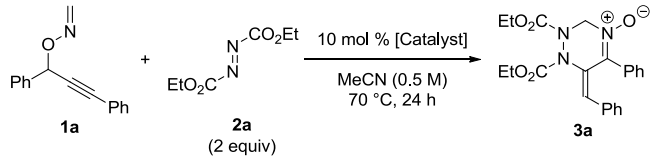


Scheme 1. Reactivity of *N*-allenylnitrone A generated from *O*-propargylic oxime 1; *N*-analog of vinylallene (type a and b), 1,3-dipolar reagent (type c), and 2-azadiene (type d, present work).

Initially, the reaction of **1a** with diethyl azodicarboxylate **2a** (2 equivalents) was carried out in the presence of a catalytic amount of CuCl (10 mol %) in acetonitrile (0.5 M) at 70 °C to afford tetrahydrotriazine **3a** in 63% yield (Table 1, entry 1). The use of

CuCl, $[CuCl(cod)]_2$, and $CuCl_2$ as the catalyst was effective, whereas CuBr and CuOTf exhibited low catalytic activities (entries 2-5). AgOTf and $RhCl(PPh_3)_3$ hardly promoted the reaction, whereas the use of $PtCl_2$ and AuCl led to complete decomposition of the starting material (entries 6-9). The reaction in the absence of a metal catalyst did not afford the desired product and 85% of starting material **1a** was recovered (entry 10). In terms of solvent effect, the use of acetonitrile was the most effective in the present reaction, whereas the use of other solvents, such as 1,4-dioxane and toluene, resulted in low chemical yields (see SI).

Table 1. Optimization of reaction conditions [a]

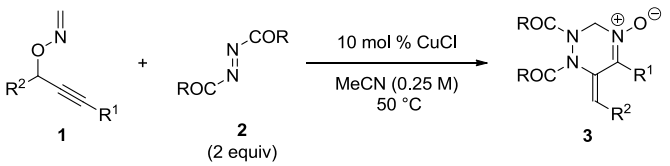


Entry	Catalyst	Yield (%)[b]	Recovery (%)[c]
1	CuCl	63	< 1
2	$[CuCl(cod)]_2$[d]	63	< 1
3	CuBr	26	< 1
4	CuOTf	44	< 1
5	$CuCl_2$	56	< 1
6	AgOTf	22	< 1
7	$RhCl(PPh_3)_3$	15	37
8	$PtCl_2$	< 1	< 1
9	AuCl	< 1	< 1
10	none	< 1	85

[a] The reaction of **1a** (0.4 mmol) with **2a** (0.8 mmol) was conducted in the presence of 10 mol % of catalyst in acetonitrile (0.8 mL) at 70 °C for 24 hours. [b] Isolated yield. [c] ^1H NMR yield using CH_2Br_2 as the internal standard. [d] 5 mol % of $[CuCl(cod)]_2$ was used.

Next, the reactivity of diazenes **2** was evaluated in the reaction of **1a** at 50 °C using CuCl as the catalyst, as summarized in Table 2. The use of a bulky ester improved the chemical yield (entries 1-3). In particular, the reaction with di-*tert*-butyl azodicarboxylate (DBAD) **2c** afforded desired product **3c** in good yield (entry 3). It should be noted that the use of 1 equivalent of **2c** resulted in a decrease of the chemical yield (entry 4). Indeed, **1a** was gradually degraded by the copper catalyst at 50 °C within one day in the absence of azodicarboxylate **2c**. Dibenzyl ester **2d**, trichloroethyl ester **2e**, and 1,1'-azodicarbonyldipiperidine (ADDP) **2f** were not effective diazenes, affording the corresponding products in poor yields (entries 5-7). Then, various *O*-propargylic formaldoximes **1** were employed as the substrate for the copper-catalyzed reaction with **2** equivalents of DBAD **2c** (entries 8-16). The reaction with substrates **1b** and **1c**, which possess an aryl substituent at the alkyne terminus (R^1), produced corresponding products **3g** and **3h**, respectively, in good yields (entries 8 and 9). Alkyl substitution at R^1 was also efficient (entries 10-12). In particular, the reaction of **1f** having a cyclohexyl group afforded desired product **3k** in an excellent yield (entry 12). The reaction of **1h** having an electron-deficient aryl group at the propargylic position (R^2) proceeded much faster than that of **1g** having an electron-rich *p*-anisyl group (entries 13 and 14). Substrate **1j** bearing an alkyl group at R^2 was also efficiently converted into product **3o** in good yield (entry 16). It is noteworthy that except **3k** and **3o**, products **3** showed only the *E* configuration at the *exo*-olefin moiety. The structures of **3** were characterized by various spectroscopic methods, such as NMR (^1H and ^{13}C), IR, and HRMS (See Supporting Information). Moreover, the structure of **3c** was unambiguously determined by X-ray crystallographic analysis, as shown in Figure 1.[13]

Table 2. Cu-catalyzed reaction of formaldoximes **1a-j** with azodicarboxylates **2**



2a (R = OEt) **2d** (R = OBn)
2b (R = O*i*Pr) **2e** (R = OCH_2CCl_3)
2c (R = O*t*Bu) **2f** (R = *N*-piperidinyl)

	1	R^1	R^2	2	Time (h)	3	Yield (%)[b]
1	**1a**	Ph	Ph	**2a**	30	**3a**	62
2	**1a**	Ph	Ph	**2b**	24	**3b**	75
3	**1a**	Ph	Ph	**2c**	10	**3c**	78
4	**1a**	Ph	Ph	**2c**[c]	10	**3c**	69
5	**1a**	Ph	Ph	**2d**	>100	**3d**	36
6	**1a**	Ph	Ph	**2e**	72	**3e**	17
7	**1a**	Ph	Ph	**2f**	26	**3f**	25
8	**1b**	*p*-$MeOC_6H_4$	Ph	**2c**	8	**3g**	78
9	**1c**	*p*-$F_3CC_6H_4$	Ph	**2c**	12	**3h**	60
10	**1d**	*n*Pr	Ph	**2c**	2	**3i**	74
11	**1e**	$H_2C{=}CH(CH_2)_2$	Ph	**2c**	6	**3j**	64
12	**1f**	Cy	Ph	**2c**	6	**3k**	94[d]
13	**1g**	Ph	*p*-$MeOC_6H_4$	**2c**	36	**3l**	77
14	**1h**	Ph	*p*-$F_3CC_6H_4$	**2c**	5	**3m**	65
15	**1i**	Ph	2-naphthyl	**2c**	12	**3n**	74
16	**1j**	Ph	*n*Pr	**2c**	30	**3o**	65[e]

[a] The reaction of **1** (0.4 mmol) with **2** (0.8 mmol) was conducted in the presence of 10 mol% of CuCl in acetonitrile (1.6 mL) at 50 °C. [b] Isolated yield. [c] 1 equivalent of **2c** was used. [d] An 85:15 mixture of *E*/*Z* stereoisomers was obtained. [e] A 66:34 mixture of *E*/*Z* stereoisomers was obtained.

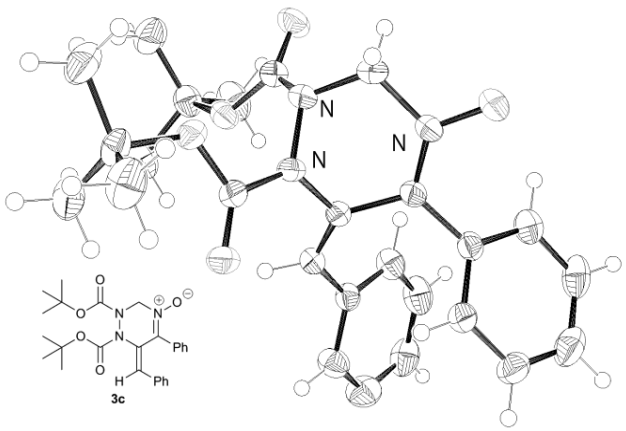
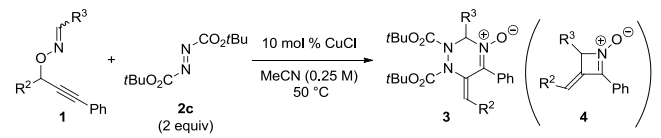


Figure 1. ORTEP drawing of **3c** (shown with 50% propability ellipsoid)

The reaction of acetaldoximes (*E*)-**1k** afforded corresponding cycloadduct **3p** in good yield (Table 3 entry 1), although prolonged reaction time was required in comparison to the formaldoxime **1a** (Table 2, entry 3). It is noteworthy that both *E* and *Z* stereoisomers of butyraldoximes **1l** and **1m** were converted into identical products **3q** and **3r**, respectively (entries 2-5). The reaction of (*Z*)-**1m** in the absence of a copper catalyst at elevated temperature (70 °C) afforded only four-membered cyclic nitrone **4m** and desired cycloadduct **3r** was not formed (entry 6).[5d] The reaction of cyclohexanecarbaldoxime required elevated reaction temperature (70 °C) to obtain **3s** in good yield (entry 7). In contrast, the reaction of benzaldoxime (*E*)-**1o** did not afford the desired product; the reaction at 50 °C resulted in the quantitative recovery of **1o**, whereas that at

100 °C solely afforded undesired four-membered cyclic nitrone **4o** (entries 8 and 9).

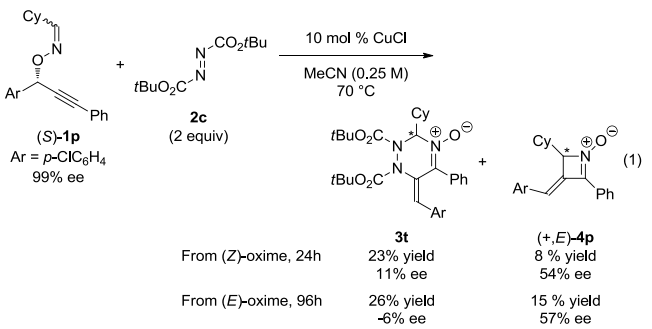
Table 3 Cu-catalyzed reaction of aldoximes **1k-o** with DBAD **2c** [a]



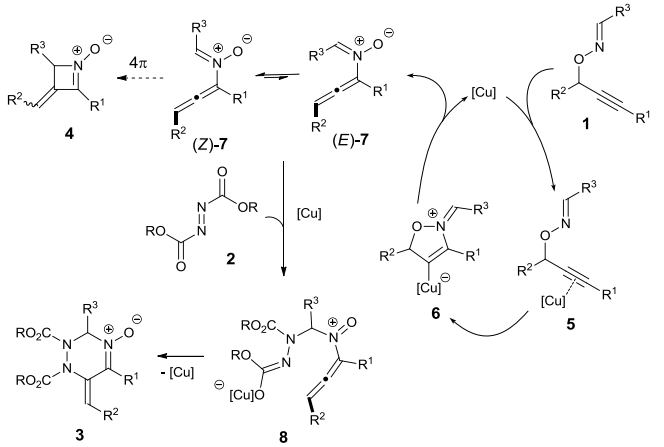
Entry	1	R^2	R^3	Time (h)	3 (%)[b]	4 (%)[b]
1	(*E*)-**1k**	Ph	Me	7 days	**3p** (78)	< 1
2	(*E*)-**1l**	Ph	*n*Pr	7 days	**3q** (77)	< 1
3	(*Z*)-**1l**	Ph	*n*Pr	48	**3q** (56)	< 1
4	(*E*)-**1m**[c]	*p*-ClC_6H_4	*n*Pr	6 days	**3r** (72)[d]	< 1
5	(*Z*)-**1m**	*p*-ClC_6H_4	*n*Pr	16[e]	**3r** (41)	< 1
6	(*Z*)-**1m**	*p*-ClC_6H_4	*n*Pr	6 days[e,f]	< 1	**4m** (48)
7	(*E*)-**1n**	Ph	Cy	100[e]	**3s** (63)	trace
8	(*E*)-**1o**	Ph	Ph	100	trace	< 1
9	(*E*)-**1o**	Ph	Ph	14[g]	< 1	**4o** (66)

[a] The reaction of **1** (0.4 mmol) with **2c** (0.8 mmol) was conducted in the presence of 10 mol % of CuCl in acetonitrile (1.6 mL) at 50 °C. [b] Isolated yield in parenthesis. [c] Chiral substrates (*S*, >99% ee) were used. [d] 2% ee. [e] At 70 °C. [f] The reaction was carried out in the absence of a copper catalyst. [g] At 100 °C.

In order to gain an insight into the reaction mechanism, the copper-catalyzed reaction of enantiomerically pure substrate (*S*)-**1p** with DBAD **2c** was carried out to afford corresponding product **3t** with excellent *E* stereoselectivity at the *exo*-olefin moiety and low enantioselectivity at the sp^3 carbon in the triazine ring, regardless of the configuration at the oxime moiety of (*S*)-**1p** (eq 1).[14,15] It should be noted that the reaction of both stereoisomers (*S*,*E*)- and (*S*,*Z*)-**1p** afforded the same enantiomer of four-membered cyclic nitrone byproduct (+,*E*)-**4p** with sufficient level of chirality transfer. Moreover, the starting material (S)-**1p** was not racemized under the reaction conditions.[16]



A plausible mechanism for the copper-catalyzed reaction between **1** and **2** is illustrated in Scheme 2. First, the π-acidic copper catalyst coordinates to the triple bond of **1**, forming π-complex **5**. Nucleophilic attack of the oxime nitrogen atom on the electrophilically activated alkyne moiety proceeds in a 5-*endo* manner, yielding cyclized vinylcopper intermediate **6**. Cleavage of the C-O bond and elimination of the copper catalyst generate *N*-allenylnitrone **7**. The nitrone carbon of key intermediate **7** nucleophilically attacks the azodicarboxylate activated by the copper catalyst, forming zwitterionic species **8**.[17] Finally, intramolecular addition of the copper amidate to the oxoammonium-conjugated C=C bond from the less hindered allene face produces **3** having an *exo*-*E*-olefin.[18] The reaction of (*Z*)-oxime in the absence of a copper catalyst afforded only four-membered cyclic nitrone **4** derived from 2,3-rearrangement followed by thermal 4π-electrocyclization (Table 3, entry 6). According to our knowledge that the 2,3-rearrangement of (*Z*)-oxime proceeds thermally, this result strongly implies that the copper catalyst promotes not only the 2,3-rearrangement but also the [4+2] cycloaddition process from **7** to **3**. The low enantioselectivity of the reaction of (*S*)-**1p** (eq 1) is presumably because azodicarboxylate **2** approaches allenylnitrone **7** from both *Si* and *Re* faces of the (*Z*)-nitrone moieties, which are far from the chiral allene group.[7a] Alternatively, loss of chirality may occur when the concerted [4+2] cycloaddition takes place from the opposite side of the chiral allene substituent (R^2) of (*Z*)- and (*E*)-allenylnitrones **7** almost equally.[19] However, the simultaneous formation of two C-N bonds is unlikely because the same enantiomer of four-membered cyclic nitrone (+,*E*)-**4p** was obtained as the byproduct of both (*Z*)- and (*E*)-**1p** with sufficient enantioselectivities, indicating that the configuration of allenylnitrone intermediate **7** is biased toward the thermodynamically more stable (*Z*)-isomer, (*Z*)-**7**.



Scheme 2. A plausible mechanism

Conclusions

In conclusion, we have developed an entirely new approach to the tetrahydrotriazine framework, which involves the catalytic cascade reaction from *O*-propargylic oximes. The key intermediate, *N*-allenylnitrone can be efficiently generated in situ by catalytic 2,3-rearrangement, in contrast to *N*-vinylnitrone, which requires several synthetic steps including the use of toxic reagents, such as aluminum amalgam and organoselenium.[8a] Therefore, the present method is useful to synthesize multisubstituted triazine derivatives in an efficient manner.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization of the products **3** and **4**. See DOI: 10.1039/c000000x/

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