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Copper-Catalyzed Aerobic Oxidative Azo-Ene Cyclization

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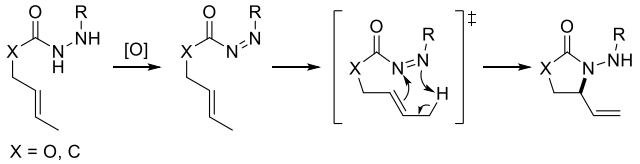
Abstract. A copper-catalyzed aerobic oxidative azo-ene cyclization has been developed. The developed CuI/DMAP/O_2 system efficiently facilitates the aerobic oxidation of ene-containing hydrazides to azo compounds, which undergo azo-ene cyclizations for the synthesis of oxazolidinones. In addition, the present approach enables the synthesis of lactams, as well as a nitroso-ene cyclization. Preliminary mechanistic studies revealed that two carbonyl groups were essential for the successful azo-ene cyclization and that a concerted mechanism might be plausible for this azo-ene cyclization.

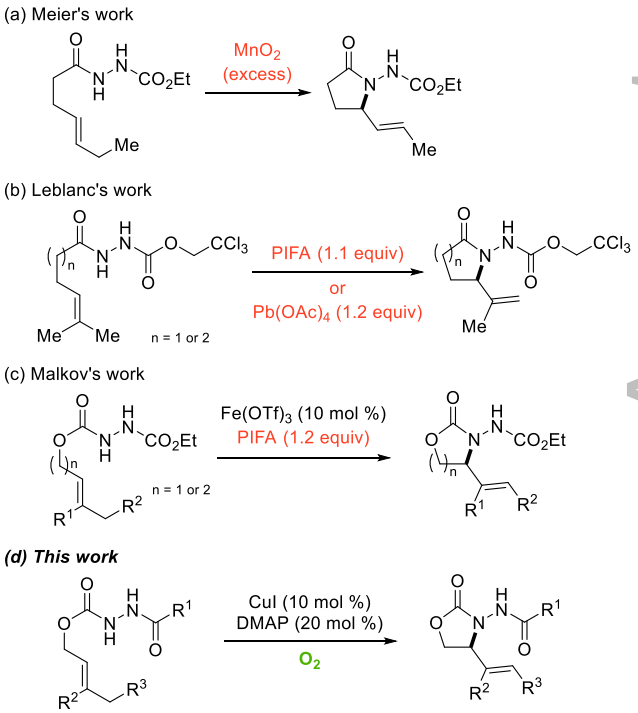
Keywords: aerobic oxidation; Cu-catalysis; azo-ene cyclization; hydrazide; organic synthesis

The ene reaction,[1] which is a pericyclic reaction between an alkene having an allylic hydrogen (ene) and multiple bonds (enophile), is of importance in organic synthesis, because the ene reaction provides facile and atom-efficient routes for the construction of chemical bonds with concomitant allylic C-H bond activation.[2] Especially, the intramolecular ene reaction (ene cyclization) is an efficient protocol for the synthesis of biologically important heterocycles.[3] A variety of multiple bonds including C=C, C=O, and C=N bonds (or their precursors) have been efficiently employed as enophiles for the synthesis of heterocycles through C-C bond formation.[4] However, the utilization of azo compounds as enophiles (azo-ene cyclization) has been relatively less investigated,[5] although the azo-ene reaction can be used for the synthesis of *N*-heterocycles bearing allylic amines through the direct C-N bond formation.[6]



Scheme 1. Mechanistic outline of the intramolecular oxidative azo-ene cyclization.

The azo-ene cyclization has been generally triggered by the oxidation of well-designed hydrazides (Scheme 1). In 1979, Meier reported that the oxidation of ethyl 2-acyl hydrazinecarboxylates by excess amounts of MnO_2 generated the corresponding azo intermediates, then the following azo-ene cyclization of the transient azo compounds produced lactams (Scheme 2 (a)).[7] The use of stoichiometric oxidants for the oxidation of acyl hydrazinecarboxylates was achieved by Leblanc and co-workers (Scheme 2 (b)).[8] When 2,2,2-trichloroethyl 2-acyl hydrazinecarboxylates were used as starting materials, the use of phenyliodine(III) bis(trifluoroacetate) (PIFA, 1.1 equiv) or $Pb(OAc)_4$ (1.2 equiv) as oxidants efficiently facilitated the oxidation of hydrazides and azo-ene cyclization sequence. Recently, the Malkov group developed an oxidative azo-ene cyclization to synthesize oxazolidinones in the presence of catalytic amounts of $Fe(OTf)_3$ and stoichiometric PIFA



Scheme 2. Representative examples of azo-ene cyclization.

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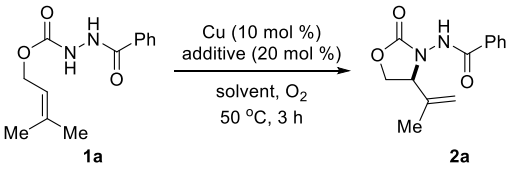
(Scheme 2 (c)).[9] Although the use of PIFA alone showed acceptable reactivity, the cleaner and accelerated azo-ene cyclization was observed by the combination of PIFA and $Fe(OTf)_3$. However, the use of molecular oxygen as an oxidant in Malkov's report gave the azo-ene reaction product in low yield.[9]

Aerobic oxidative transformations exhibit a number of advantages over other oxidation reactions with organic or inorganic oxidants.[10] Compared to other oxidants, molecular oxygen is inexpensive and readily accessible. In addition, only water is produced as a byproduct, therefore, no laborious purification processes are required. Recently, we, and other groups, have developed several reaction systems to carry out aerobic oxidations of disubstituted hydrazines.[11,12] Notably, our developed CuI/DMAP system was effective for the oxidation of hydrazinedicarboxylates, which have high oxidation potentials.[11a,13] Building from our previous work, and inspired by the reports described above, we envisioned that the aerobic oxidative azo-ene cyclization of hydrazinedicarboxylates containing an ene moiety might be possible. Herein, we describe a Cu-catalyzed aerobic oxidative azo-ene cyclization for the synthesis of oxazolidinones (Scheme 2 (d)).

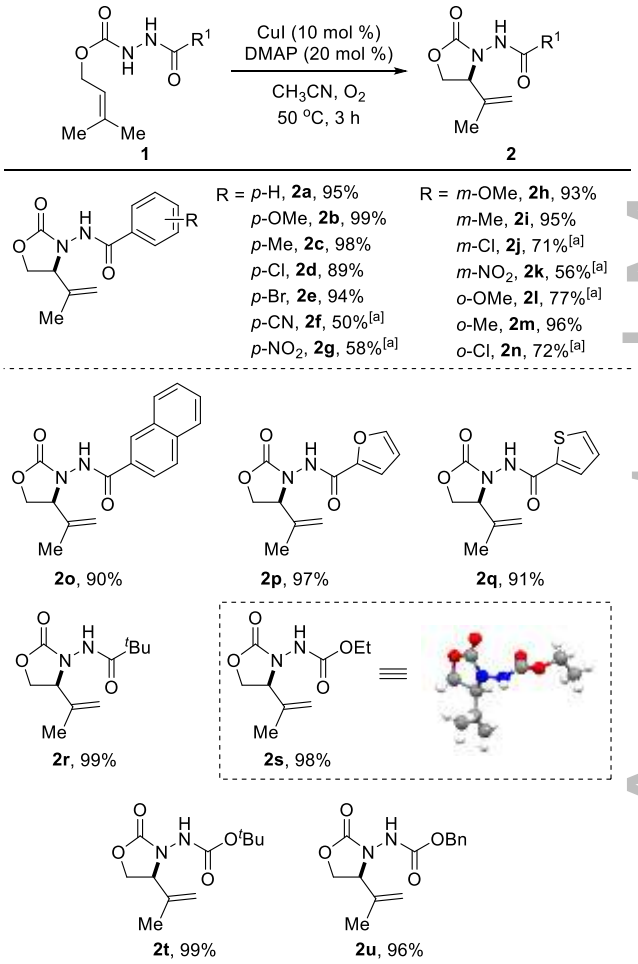
Table 1. Optimization of the Cu-catalyzed aerobic oxidative azo-ene cyclization.[a]



entry	Cu	additive	solvent	yield (%)[b]
1	CuI	DMAP	CH_3CN	99
2	CuBr	DMAP	CH_3CN	90
3	$CuBr_2$	DMAP	CH_3CN	89
4	$Cu(CH_3CN)_4PF_6$	DMAP	CH_3CN	0
5	$Cu(OAc)_2$	DMAP	CH_3CN	7
6	$Cu(OTf)_2$	DMAP	CH_3CN	10
7	CuI	pyridine	CH_3CN	4
8	CuI	4-OMepy	CH_3CN	14
9	CuI	1,10-phen	CH_3CN	15
10	CuI	DMAP	toluene	12
11	CuI	DMAP	DMSO	33
12[c]	CuI	DMAP	CH_3CN	28,90[d]
13	CuI	DMAP	CH_3CN	8[e]
14[f]	CuI	DMAP	CH_3CN	51,92[d]

[a]Reaction conditions: **1a** (0.5 mmol), Cu (10 mol %), and additive (20 mol %) in solvent (3.0 mL) under an O_2 balloon at 50 °C for 3 h. [b]Yield of **2a** was determined by ^1H NMR spectroscopy with 1,1,2,2-tetrachloroethane as internal standard. [c]Under air. [d]For 15 h. [e]At room temperature. [f]The use of 5 mol % of Cu and 10 mol % of DMAP.

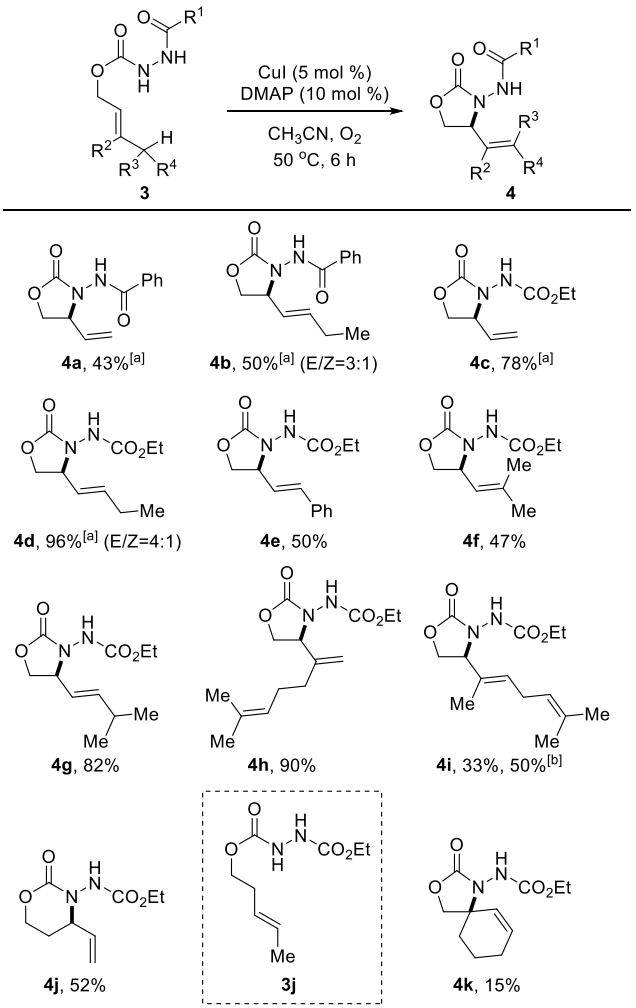
Initially, 3-methylbut-2-en-1-yl 2-benzoylhydrazinecarboxylate (**1a**) was selected as a model substrate to explore the feasibility of our envisioned Cu-catalyzed aerobic oxidative azo-ene cyclization (Table 1).[14] Gratifyingly, the use of CuI and 4-(dimethylamino)pyridine (DMAP), which was an efficient catalyst system for the aerobic oxidations of di-*tert*-butyl hydrazodicarboxylates,[11a] generated the desired oxazolidinone (**2a**) in a quantitative yield (entry 1). Among the copper catalysts screened, it was observed that cuprous or cupric halides facilitated the present azo-ene cyclization, albeit in slightly inferior yields to CuI (entries 2–3). However, the azo-ene cyclizations with other copper salts such as $Cu(CH_3CN)_4PF_6$, $Cu(OAc)_2$, and $Cu(OTf)_2$ showed poor reactivity (entries 4–6). It was revealed that the use of DMAP is superior to other additives including pyridine, 4-methoxypyridine (4-OMepy), and 1,10-phenanthrolrine (1,10-phen) (entries 7–9). No reasonable yields were observed in the use of other solvents (entries 10–11). It is worth noting that the present cyclization could also be carried out under air (entry 12). The yield of **2a** was lowered to a greater



Scheme 3. Substrate scope of substitution at the R^1 position in hydrazinecarboxylates **1**. Reaction conditions: **1** (0.5 mmol), CuI (10 mol %), and DMAP (20 mol %) in CH_3CN (3.0 mL) under an O_2 balloon at 50 °C for 3 h. Isolated yield. [a]At 70 °C for 15 h.

extent at room temperature (entry 13). The catalyst loading could be reduced to 5 mol % of CuI and 10 mol % of DMAP, however, increased reaction time was required to obtain an acceptable product yield (entry 14). Control experiments revealed that the use of Cu, DMAP, and molecular oxygen was indispensable for the successful azo-ene cyclization.[14] The use of hydrogen peroxide (1.0 equiv) as an oxidant[9,15] under molecular nitrogen produced **2a** in 22% yield.[14]

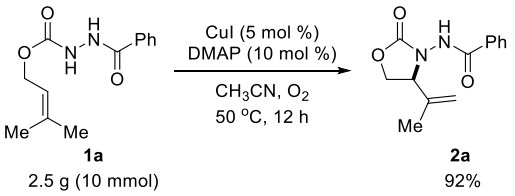
With the optimized conditions in hand (Table 1, entry 1), we next explored the scope of substitution at the R^1 position in hydrazinecarboxylates **1** (Scheme 3). It was observed that the cyclization of 3-methylbut-2-en-1-yl 2-benzoylhydrazinecarboxylates having electron donating groups on the phenyl moiety produced the corresponding oxazolidinones in high yields under the optimized conditions (**2a**–**2e**, **2h**–**2j**, and **2l**–**2n**), however, that of 3-methylbut-2-en-1-yl 2-benzoylhydrazinecarboxylates bearing electron withdrawing groups required a longer reaction time at elevated temperature (**2f**, **2g**, and **2k**). Other



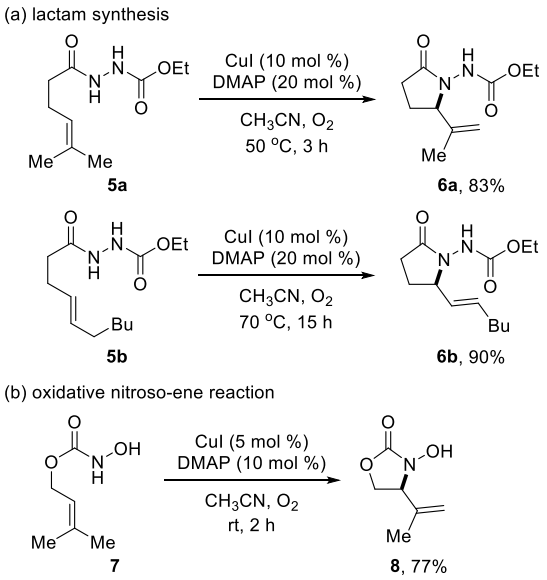
Scheme 4. Substrate scope of ene group. Reaction conditions: **3** (0.5 mmol), CuI (5 mol %), and DMAP (10 mol %) in CH_3CN (3.0 mL) under an O_2 balloon at 50 °C for 6 h. Isolated yield. [a]The use of CuI (10 mol %) and DMAP (20 mol %) at 70 °C for 15 h. [b]The use of CuI (10 mol %) and DMAP (20 mol %) at 50 °C for 3 h.

oxazolidinones having naphthalene, furan, or thiophen group were also efficiently synthesized by our method (**2o**–**2q**). A pivaloyl group was tolerable in the developed reaction conditions to derive a high yield (**2r**). Interestingly, it was shown that alkoxy carbonyl substrates showed excellent yields regardless of alkoxy groups (**2s**–**2u**). The structure of the desired product **2s** was unambiguously characterized by X-ray crystallography.[16]

Next, the substrate scope of the ene group was investigated with the slight modification of the optimized conditions (Scheme 4). Both substrate **3a** and substrate **3b**, which were synthesized from crotyl alcohol and trans-hex-2-enol respectively, showed moderate yields even with higher catalyst loading, whereas the derivatives of ethoxy carbonyl **3c** and **3d** exhibited better reactivity. It was observed that the oxazolidinones **4b** and **4d** were produced as 3:1 and 4:1 E/Z mixtures, respectively. The azo-ene cyclization of hydrazides bearing other allylic alcohols such as 4-phenyl-2-butenol, 4-methyl-2-pentenol, and 5-methyl-2-hexenol produced the corresponding oxazolidinones in moderate to good yields (**4e**–**4g**). Although the hydrazide derived from nerol showed good reactivity, the azo-ene cyclization of the hydrazide derived from geraniol was sluggish (**4h** and **4i**). Interestingly, it was shown that the formation of a six-membered ring was accessible through the present azo-ene cyclization of **3j** (**4j**). However, the azo-ene cyclization of **3k** for the synthesis of spiro oxazolidinone produced **4k** in 15% yield with



Scheme 5. Scale-up process for the aerobic oxidative azo-ene cyclization.



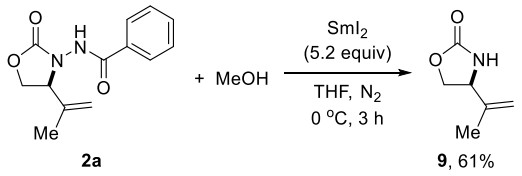
Scheme 6. Cu-Catalyzed aerobic oxidative synthesis of lactams and nitroso-ene cyclization.

numerous unidentified side products.

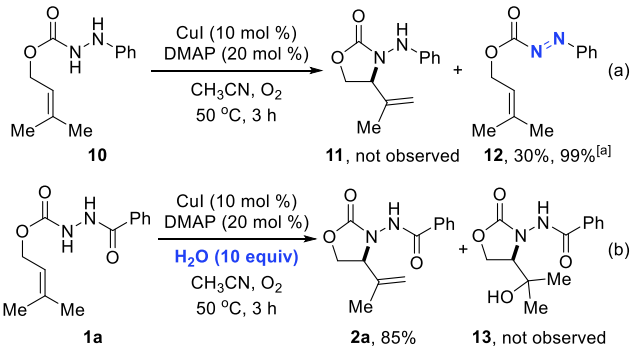
We carried out the aerobic oxidative azo-ene cyclization of **1a** on a 20-fold scale to highlight the practicality of the developed protocol (Scheme 5). By reducing the catalyst loading and increasing the reaction time, we were able to achieve the large scale azo-ene cyclization with no significant decrease to either the conversion or the yield.

It was demonstrated that the developed CuI and DMAP system facilitated the synthesis of lactams. When ethyl 2-(5-methylhex-4-enoyl)hydrazinecarboxylate **5a** and ethyl 2-(dec-4-enoyl)hydrazinecarboxylate **5b** were exposed to the developed reaction conditions, the desired products **6a** and **6b** were produced in high yields (83% and 90%, respectively) (Scheme 6 (a)).[17] In addition, the present protocol was able to be applied to the aerobic oxidative nitroso-ene cyclization.[6,18] Using slightly modified reaction conditions (including reduced catalyst loading, room temperature, and shorter reaction time) enabled the aerobic oxidative nitroso-ene cyclization of *N*-hydroxycarbamate **7** to produce the desired product **8** in 77% yield (Scheme 6 (b)).[19]

Cleavage of the N-N bond in the oxazolidinone products could be achieved by the previously reported procedure (Scheme 7).[20] In the presence of SmI_2 in MeOH, the N-N bond in the oxazolidinone **2a** underwent cleavage to afford **9** in 61% yield.



Scheme 7. Cleavage of the N-N bond.



Scheme 8. Mechanistic investigation for the aerobic oxidative azo-ene cyclization. [a]At room temperature for 2 h.

In order to obtain mechanistic insight into our developed protocol, we tried to isolate the azo compounds, which would be the presumed intermediates of the cyclization. However, the azo compounds were not observed during our optimization and substrate scope study. Instead, when 3-methylbut-2-en-1-yl 2-phenylhydrazinecarboxylate **10** was used as a starting material in the developed reaction conditions, the azo compound **12** was produced in 30% yield along with other decomposition products, and no cyclization product **11** was produced (Scheme 8 (a)).[21] Quantitative yield of azo compound **12** was obtained in the reaction of **10** at room temperature after 2 hours These results indicate that two carbonyl groups of hydrazides, which makes the azo enophile electron-deficient, was shown to be essential for the successful azo-ene cyclization, and indirectly support that the azo compound is a key intermediate during azo-ene cyclization. The addition of 10 equivalent of water to the optimized conditions did not generate the Prins-type byproduct **13**, and only a slight reduction to the yield was observed (Scheme 8 (b)). Therefore, a concerted mechanism might be the plausible mechanism for the present azo-ene cyclization, however, other possibilities such as stepwise mechanism could not be completely ruled out at this stage.[2b] Thus, we proposed that the overall mechanism consist of a Cu-catalyzed aerobic oxidation of the hydrazinecarboxylate followed by an azo-ene cyclization.[22]

In conclusion, we have developed a novel aerobic oxidative azo-ene cyclization for the synthesis of oxazolidinones. Not only various ene groups but also carbonyl substituents such as benzoyl, hetero-aroyl, acyl, and alkoxy carbonyl could be employed to produce the corresponding oxazolidinones. The present approach was effective even on a larger scale, and enabled the synthesis of lactams and also a nitroso ene cyclization. Preliminary mechanistic studies revealed that two carbonyl groups were essential to activate the azo enophile and that the azo-ene cyclization likely occurs with a concerted mechanism. Further studies to understand mechanistic details for the present aerobic oxidative azo-ene reaction are underway.

Experimental Section

General Procedure for the Synthesis of Products 2: A 10 mL flame-dried test tube (O.D. 15 mm), which was equipped with a magnetic stir bar and charged with the hydrazide **1** (0.5 mmol), CuI (10 mol %, 0.05 mmol), and DMAP (20 mol %, 0.1 mmol) was evacuated and backfilled with oxygen (this process was repeated three times). After acetonitrile (3.0 mL) was added, the reaction mixture was stirred at 50 °C. After 3 h, the mixture was quenched with a saturated aqueous solution of NH_4Cl at room temperature and diluted with DCM. Two layers were separated, and aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated on rotary evaporator. The residue was purified by column chromatography to give products **2**.

Acknowledgements

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Basic Science Institute for the technical support in the SC-XRD analysis.

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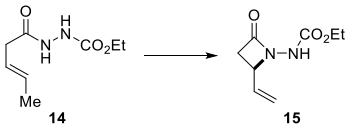
[16] CCDC-2060272 (**2s**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] We attempted the Cu-catalyzed aerobic azo-ene cyclization of **14** for the synthesis of β-lactam **15**, however, no conversion of **14** was observed.



14 **15**

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[21] With the isolated azo compound **12**, we have tested the cyclization of **12** in the presence of Lewis acid (1.5 equiv) such as $AlCl_3$, $FeCl_3$, and $Cu(OTf)_2$, however, no cyclization product **11** and the decomposition of **12** were observed.

[22] The used copper might also facilitate the azo-ene cyclization as a Lewis acid.

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