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COMMUNICATION

Cu-catalyzed Oxygenation of Alkene-tethered Amides with O_2 via Unactivated C=C Bond Cleavage: A Direct Approach to Cyclic Imides

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The transformations of unactivated alkenes through C=C bond double cleavage are always attractive but very challenging. We report herein a chemoselective approach to valuable cyclic imides by a novel Cu-catalyzed geminal amino-oxygenation on the unactivated C=C bonds. O_2 was successfully employed as the oxidant as well as the O-source, and was incorporated into alkenyl amides via C=C bond cleavage for the efficient preparation of succinimide or glutarimide derivatives. Moreover, the present strategy under simple conditions can be used in the late-stage modification of biologically active compounds and the synthesis of pharmaceuticals, which demonstrated the potential application.

The 5- and 6-membered cyclic imide moiety is frequently present as the key subunit in substantial pharmaceuticals and bioactive compounds[1] (Figure 1). For instance, the 5-membered cyclic imides (succinimides) **i**, **ii** and **iii** are commonly used to treat petit malepilepsy,[2] while the 6-membered cyclic imides (glutarimides) **iv**, **v**, and **vi** could be used as sedative-hypnotics,[3] antineoplastic and immunomodulatory drugs.[4] Interestingly, the penitential thalidomide **vi** has returned to the market as the treatment of cancer under the brand name Immunoprin,[5] since the conviction of the culprit of phocomelia in 1960s.[6] The evolution of synthetic methods for cyclic imides is continuously driven forward by their importance in medicinal chemistry. Typical methods for the synthesis of simple imides include the ammonolysis of anhydrides under high temperature,[7] the oxidation of lactams with strong or special oxidants,[8] and the reduction of unsaturated imides such as maleimide,[9] or metal-catalyzed carbonylation of various precursors.[10] However, the approaches to polysubstituted cyclic imides remains

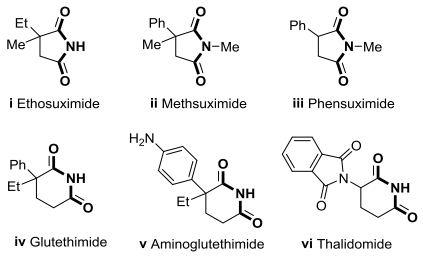

Figure 1. Some pharmaceuticals with succinimide and glutarimide moieties.

challenging due to tedious transformations that are required for the preparation of anhydride precursors.

It is instructive that the difunctionalization of alkenes is such a versatile transformation for the assembly of two individual functional groups across C=C double bonds.[11] Alkene-tethered amides, which serve as the substrates for intramolecular amidation of unactivated alkenes initiated by the photo-induced amidyl radical formation or metal-mediated amidocyclization, have emerged as the ideal precursor of γ-lactams in recent years with well established transformations[12] (Scheme 1 a1).

Recently, O_2 or air has been regarded as an ideal oxidant because of its inexpensive, environmentally benign and high atom economy characteristics, which attracts academic and industrial attentions.[13] The oxygenations of olefins enable efficient protocols for the construction of epoxides,[14] diols,[15] and ketones[16] with/without C=C double bond cleavage.[17] Given what we discovered in our previous studies on the oxygen mediated C=C bond cleavage,[18] we proposed that the geminal olefin amino-oxygenation of pent-4-enamides via chemoselective C=C double bond cleavage, would be highly promising to produce succinimides in the presence of oxygen (Scheme 1b). To date, the aerobic oxidation of enamides has only been documented in the Pd(II)-catayzed intramolecular aza-Wacker-type cyclization.[19] Recently, a significant aminooxygenation 4-pentenylsulfonamides was reported by Chemler and coworkers (Scheme 1 a2),[20] in which the C=C bond cleavage were successfully achieved but by two steps. The DABCO was required as a base with the formation of γ-lactam products. To the best of our knowledge, the

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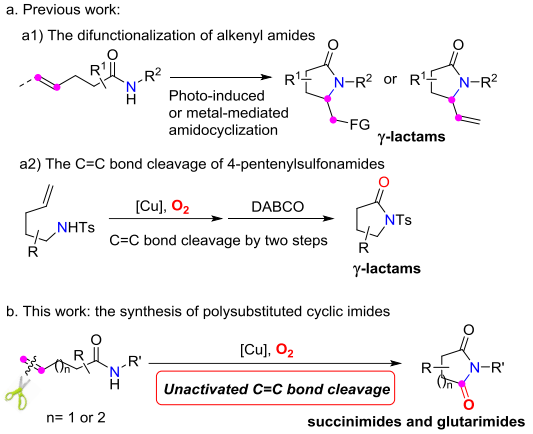
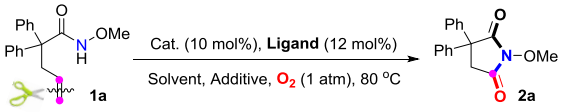
chemoselective cleavage of C=C double bonds in alkene-tethered amides for cyclic imides synthesis has not been accomplished yet.



Scheme 1. The strategies for the oxygenation of unactivated alkenyl amides.

Our investigation commenced with *N*-methoxy alkenyl amide **1a**. After a lot of experiments, we were surprised to find that the containing unactivated C=C double bond could be cleaved with the incorporation of one oxygen atom by O_2. Encouraged by the copper catalyzed olefin amino-oxygenation which delivered **2a** in 47% yield (Table 1, entry 1), a variety of conditions were screened (see SI). The control experiments demonstrated that the reaction could not work in the absence of copper catalyst, or oxygen atmosphere (Table 1, entries 2-3). Besides, different copper catalyst, solvents, additives and ligands were also screened (Table 1, entries 5-10). The yields were sharply decreased when bases or acids were used as additives. Finally, we found that the reaction with copper acetate as the catalyst, bathocuproine (**Ligand II**) as ligand in toluene executed the unactivated C=C double bond geminal amino-oxygenation reaction well and produced the desired succinimide product **2a** in excellent efficiency (83% isolated yield, Table 1, entry 10).

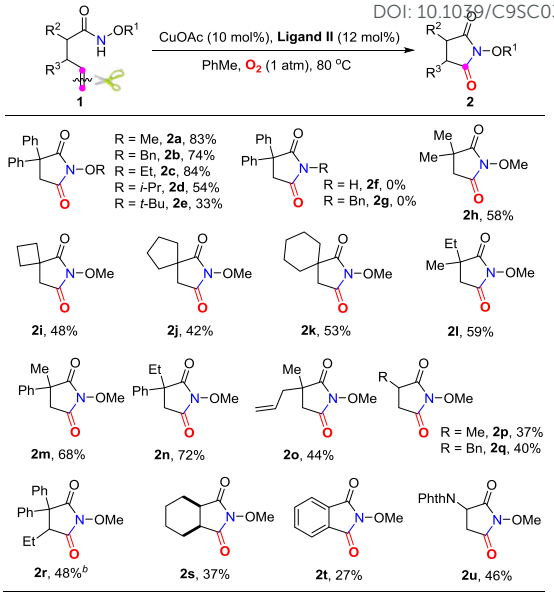
Table 1. Screening of reaction conditions[a]



entry	catalyst	ligand	solvent	additives	yield (%)[b]
1	$Cu(OAc)_2$	1,10-phenanthroline	PhMe	--	47
2	--	1,10-phenanthroline	PhMe	--	nd[d]
3[c]	$Cu(OAc)_2$	1,10-phenanthroline	PhMe	--	nd
4	$Cu(OAc)_2$	--	PhMe	--	13
5	CuOAc	1,10-phenanthroline	PhMe	--	53 (60)
6	CuOAc	1,10-phenanthroline	$PhCF_3$	--	66
7	CuOAc	bathocuproine	$PhCF_3$	--	82
8	CuOAc	bathocuproine	$PhCF_3$	K_2CO_3	10
9	CuOAc	bathocuproine	$PhCF_3$	$PhCO_2H$	52
10	CuOAc	bathocuproine	PhMe	--	81 (83)
11	CuOAc	bathocuproine	PhMe	--	(80)[e]

[a] Reaction conditions: **1a** (0.2 mmol), catalyst (0.02 mmol), ligand (0.024 mmol) and additive (1.0 equiv.) were stirred in solvent (2.0 mL) at 80 ℃ under O_2. [b] Determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as internal standard. The numbers in parentheses are isolated yields. [c] Under argon atmosphere. [d] Not detected. [e] This reaction was carried out under air.

Table 2. Substrate scope for the synthesis of succinimides[a]



[a] Reaction conditions: see entry 10, Table 1. Isolated yields. [b] Reaction for 48 hours.

Subsequently, a good number of pent-4-enamides were smoothly converted to succinimides in moderate to good yields (Table 2). Several *N*-alkoxy protecting groups were well tolerated (up to 84%, **2a**-**2c**) while substrates bearing bulky groups were inferior (**2d**, **2e**). When hydrogen atom (**2f**) or benzyl group (**2g**) attached to the amide nitrogen, the reaction did not work. The reason is that the alkyl–metal intermediates formation might be favored in the assistance of alkoxy protecting group.[12d, 12e] α-Geminal substituted substrates worked well in this transformation (Table 2, **2h**-**2o**), producing polysubstituted and spiro-succinimides in moderate to good yields. It is noteworthy that the reaction could contain one of the identical allyl groups specifically to give the allylic imide in 44% yield (**2o**). The mono methyl or benzyl substituted enamides were also tolerated, and the desired products could be obtained in fair yields (**2p** and **2q**). To our delight, the vinylcyclohexane derived enamide underwent the process smoothly to afford the corresponding imide **2s**. The 2-vinylbenzamide was also compatible to give the synthetic important phathlimide **2t** albeit the efficiency is a little bit low, because the conjugated alkenes would undergo un-wanted oxidation. Unfortunately, the alkene-tethered amide without alkylation on the backbone did not work. Notably, the glutarimide derivatives **4a**-**4d** were also obtained in moderate yields with hex-5-enamides (Table 3).

To demonstrate the synthetic value of our strategy, several late-stage modifications of biologically active compounds were carried out under the standard conditions (Scheme 2).

Table 3. Substrate scope for the synthesis of glutarimides[a]

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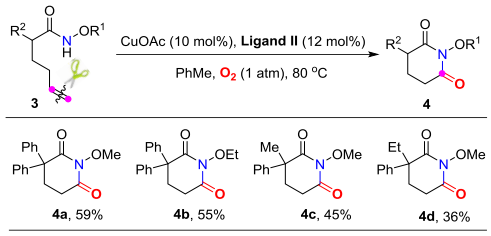
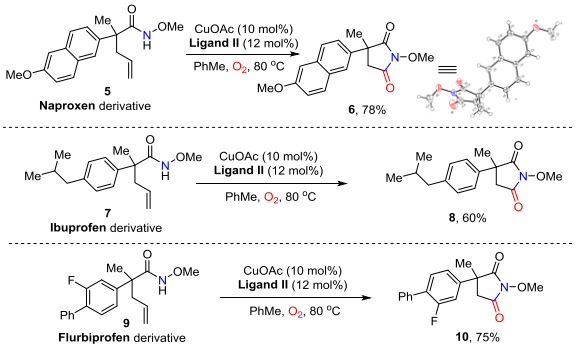
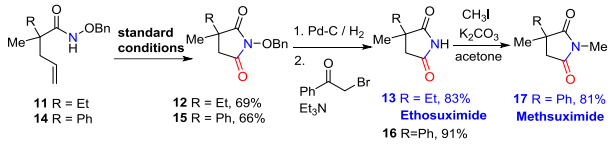


[a] Reaction conditions: see entry 10, Table 1. Isolated yields.



Scheme 2. Application in the synthesis of drug analogues.

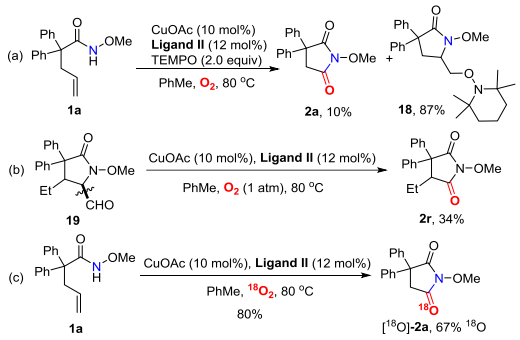


Scheme 3. Synthesis of succinimide-containing medicines.

Naproxen, approved by the USA Food and Drug Administration (FDA) for anti-inflammation, antipyretics and analgesics, could deliver succinimide **6** in 78% yield via analogue **5** under the standard conditions (Scheme 2). The structure of **6** was confirmed by X-ray single crystal structural analysis. Additionally, the derivatives of best-seller drugs Ibuprofen and Flurbriprofen could also undergo the present transformation to afford the desired product **8** in 60% yield and **10** in 75% yield respectively. These results provide efficient approaches to drug analogues for future medicinal chemistry studies.

Furthermore, our strategy can be applied to the synthesis of two pharmaceutical compounds Ethosuximide **i** and Methsuximide **ii** (Figure 1). As shown in Scheme 3, the amidocyclization of **11** gave *N*-benzyloxy succinimide **12** in 69% yield under the standard conditions, followed by the removal of the *N*-benzyloxy group by hydrogenation and treatment of 2-bromoacetophenone and triethylamine to furnish[21] the Ethosuximide in high yield (**13**, 83%), which possess antiepileptic effect. This method avoids the use of highly toxic hydrocyanic acid in industrial production. Similarly, the Methsuximide **17** could also be obtained from the succinimide **15** in good overall yield.

In order to probe the mechanism, some control experiments were designed and investigated (Scheme 4). Firstly, the reaction was conducted in the presence of TEMPO as a radical scavenger, and the difunctionalization product **18** could be obtained in 87% yield, with the formation of **2a** in only 10% yield (Scheme 4a). This result indicates that an alkyl radical intermediate was produced after the intramolecular amido-cyclization process. Then, to investigate the intermediacy of aldehyde in the C=C bond cleavage, 2-pyrrolidinone **19** was employed under standard conditions. The formation of **2r** with some unconsumed raw materials compared with the result in Table 2 indicate that the aldehyde might be involved in this transformation (Scheme 4b). In addition, the isotopic labeling studies under $^{18}O_2$ delivered the labeled succinimide [^{18}O]-**2a** in



Scheme 4. Mechanistic studies.

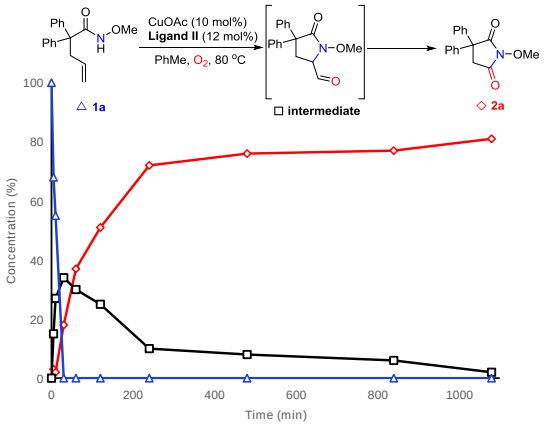
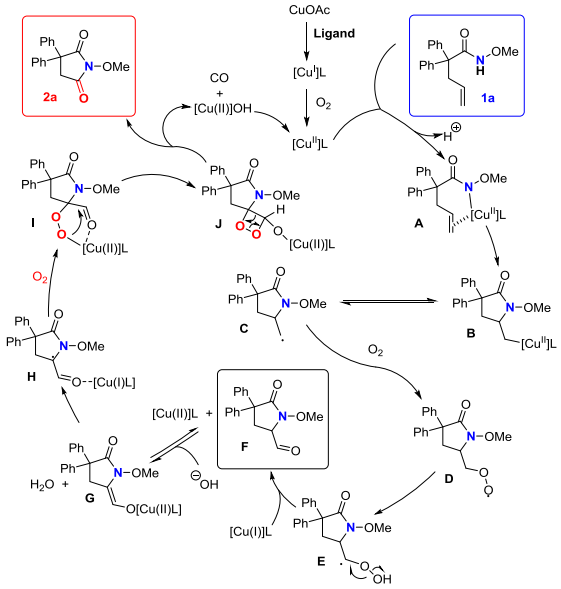


Figure 2. Kinetic profile of this C=C bond oxygenation reaction.

80% yield (67% ^{18}O) due to the exchange with H_2O (see SI), which supports our expectation. We also studied the reaction kinetic profile, which showed the initial increase and later consumption of aldehyde intermediate along with the formation of succinimide (Figure 2). This result was in accordance with our aforementioned observation. The tentative studies on trapping intermediates were also carried out by EPR (see SI).

Based on previous reported[12e, 20] and our own mechanistic studies, a plausible mechanism is shown in Scheme 5. We proposed that copper(I) is oxidized to copper(II) by O_2 in the initial step. Then, copper(II)-catalyzed alkene *cis*-amidocupration affordes an unstable organocopper(II) intermediate **B**. Primary radical **C** which could be trapped by TEMPO (Scheme 4a), is subsequently generated by the C–Cu homolysis of intermidiate **B**.[22] The mechanism is not completely clear yet. Alternatively, the lack of detection of the amidyl radical by EPR analysis (see SI) could not fully disprove its presence under the reaction conditions. The primary radical **C** may also be generated by the addition of amidyl radical to the double bond. Then, the radical species **C** is trapped by

molecular oxygen and produces the superoxide radical **D**. Then, the intramolecular 1,3-hydrogen migration occurs to form the intermediate **E**, followed by the O–O homolysis to give the aldehyde **F** and hydroxyl radical which is unstable and easily reduced *in situ* to give hydroxide anion. The intermediate aldehyde **F** could be directly transformed into copper(II) enolate **G** which undergoes formal [2+2] cycloaddition of another molecule of oxygen to give the 1,2-dioxetane **J** *via* radical species **H** and cyclic peroxo intermediates **I**.[23] Then the ring opening process occurs to form the succinimide **2a** and released carbon monoxide.



Scheme 5. Proposed mechanism of the reaction.

In summary, we developed a novel molecular oxygen mediated geminal amino-oxygenation of unactivated olefin in the alkene-tethered amides via a chemoselective cyclization/C=C bond cleavage processes that revealed an efficient approach to polysubstituted succinimides and glutarimides. Our reaction exhibited good functional group tolerance under simple conditions. The success of this protocol in the late-stage modification of biologically active compounds and the synthesis of pharmaceuticals would motivate further exploration in the transformations of unactivated alkenes.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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