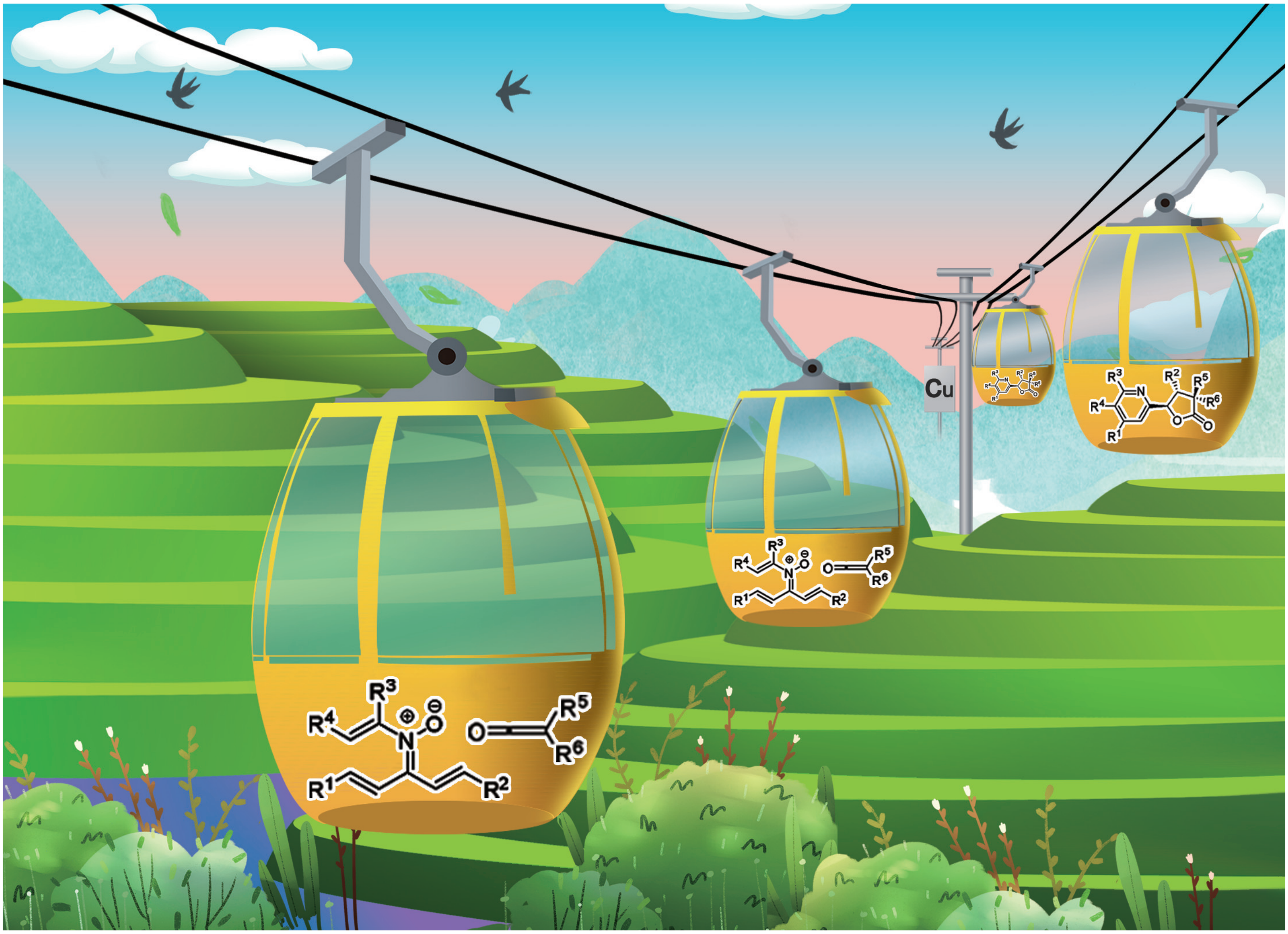

An article presented by Prof. Dong-Liang Mo *et al.* of the Guangxi Normal University, People's Republic of China.

A copper-catalyzed diastereoselective O-transfer reaction of *N*-vinyl-*N*α,β-unsaturated nitrones with ketenes into γ-lactones through [5 + 2] cycloaddition and N–O bond cleavage

A copper-catalyzed atom economic O-transfer reaction strategy was developed for the synthesis of densely functionalized *O*γ-lactones from *N*-vinyl-α,β-unsaturated nitrones and ketenes.

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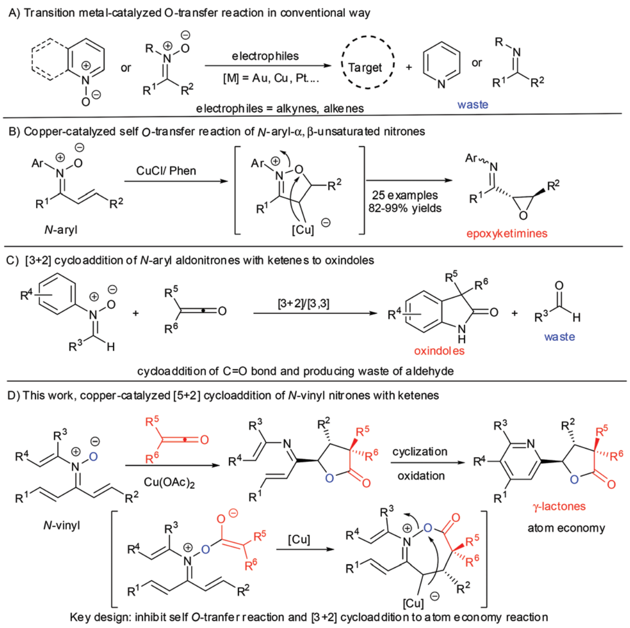
A copper-catalyzed diastereoselective O-transfer reaction of *N*-vinyl-α,β-unsaturated nitrones with ketenes into γ-lactones through [5 + 2] cycloaddition and N–O bond cleavage†

Jun-Yi Liao,‡[a] Qing-Yan Wu,‡[a] Xiuqiang Lu,[b] Ning Zou,[a] Cheng-Xue Pan,[a] Cui Liang,[a] Gui-Fa Su*[a] and Dong-Liang Mo *[a]

A general protocol for the construction of novel densely functionalized γ-lactones was developed in good to excellent yields with high diastereoselectivity from easily available *N*-vinyl-α,β-unsaturated nitrones and ketenes. The reaction involves copper-catalyzed [5 + 2] cycloaddition, N–O bond cleavage, 6π electron cyclization, and aromatization to afford various γ-(pyridin-2-yl)lactones over four step transformations in a single flask. The present method features mild reaction conditions, high atom economy, high regio- and diastereoselectivity, diversity of γ-lactones, and a new application of the O-transfer reaction.

γ-Lactones are valuable heterocycles that are not only found in a large number of biologically active natural and unnatural molecules but also serve as versatile synthetic intermediates to access many important architectures, such as 1,4-diols, γ-hydroxycarboxylic acids, and tetrahydrofurans.[1] Naturally occurring γ-lactones are often present in various pharmaceuticals, foods and fruits and show interesting biological activities.[2] Many elegant strategies for synthesizing γ-lactones have been reported, including oxyfunctionalization of alkenes,[3] dehydrogenative esterification,[4] C–H activation,[5] hydroacylation or hydrohydroxyalkylation,[6] ring-opening and rearrangement reactions,[7] and other cascade transformations.[8] Unfortunately, the corresponding methods for the preparation of densely functionalized γ-lactones are sparse and no reported strategy has been shown to construct γ-(pyridin-2-yl)lactones containing pyridine and γ-lactone rings in a one pot reaction. Consequently, exploring a general and practical method for the preparation of densely functionalized γ-lactones would facilitate the study of biological activity of these compounds.

The transition-metal catalyzed O-transfer reaction of N–O bond compounds, such as pyridine *N*-oxides, nitrones, and oxime ethers, provides a good tool to introduce an oxygen source into complex target molecules.[9] However, the generated N-heterocycles or imines from *N*-oxides or nitrones in most of these reactions usually did not participate in the reaction and were left as waste (Scheme 1-A). The atom economical reaction is one of the most important goals in green chemistry because it does not produce additional waste and improves the synthetic efficiency. Consequently, development of an atom economical O-transfer reaction is valuable. In 2013, Anderson and coworker pioneered the development of a copper-catalyzed



Scheme 1 New application for the copper-catalyzed O-transfer reaction of α,β-unsaturated nitrones to γ-lactones.

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† Electronic supplementary information (ESI) available: Experimental details and characterization of all compounds and copies of ^{1}H and ^{13}C NMR for new compounds. CCDC 1915597. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/C9GC01811E

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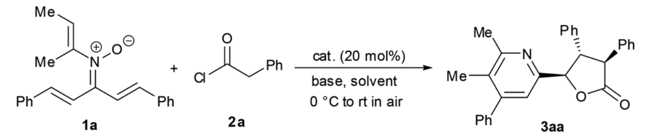
self O-transfer reaction of *N*-aryl-α,β-unsaturated nitrones to prepare useful α,β-epoxyketimines and a plausible isoxazoline intermediate was proposed (Scheme 1-B).[10] This strategy showed an efficient and atom economical O-transfer reaction and demonstrated the distinct reactivity and powerful application of *N*-aryl-α,β-unsaturated nitrones. But this self intramolecular O-transfer reaction still limited its application to more complex motifs. *N*-Substituted-α,β-unsaturated nitrones as useful organic building blocks have attracted much attention because the double bond of nitrones can participate in many transformations to construct complex molecules.[11] Since the pioneering observations of [5 + 2] cycloaddition of *N*-aryl-α,β-unsaturated nitrones with activated alkynes by the Yang group,[12] many cycloadditions of *N*-substituted-α,β-unsaturated nitrones with various dipolarophiles to prepare complex heterocycles were reported.[13] However, most of these reactions involved [3 + 2] cycloaddition instead of [5 + 2] cycloaddition. The regioselectivity between [3 + 2] and [5 + 2] cycloaddition of α,β-unsaturated nitrones with different dipolarophiles is still unresolved and challenging.

Ketenes, generated from acyl chlorides or their equivalents, are useful and important reactive intermediates in organic synthesis and participate in various cycloadditions.[14] However, to date, the cycloaddition of nitrones with ketenes has usually provided oxindoles and produced aldehyde as waste, showing that the cycloaddition of ketenes occurred at the C═O bond (Scheme 1-C).[15] To avoid these drawbacks, [3 + 2] cycloaddition occurring at the C═O bond of ketenes should be inhibited. During studies of the preparation and cycloaddition of α,β-unsaturated nitrones in our group,[16] recently, we have reported an iron(III) catalyst controlled selective cyclization of *N*-vinyl-α,β-unsaturated nitrones to prepare polysubstituted pyridines and isoxazolines in good to excellent yields.[16a] Then, we proposed that using ketenes generated from acyl chlorides under base conditions as dipolarophiles in the cycloaddition would inhibit the self O-transfer reaction of α,β-unsaturated nitrones due to their high reactivity to be attacked fast by the O-atom of nitrones. And the metal-catalyst subsequently coordinated to the double bond would facilitate [5 + 2] cycloaddition instead of [3 + 2] cycloaddition to afford new heterocyclic scaffolds through subsequent metal-catalyzed N–O bond cleavage (Scheme 1-D). Herein, we describe our design for a new application of the O-transfer reaction through copper-catalyzed [5 + 2] cycloaddition of *N*-vinyl-α,β-unsaturated nitrones with ketenes to prepare a variety of γ-(pyridin-2-yl)lactones and γ-ketolactones in good to excellent yields over four step transformations in a one-pot reaction under air conditions.

Our investigations started with *N*-vinyl-α,β-unsaturated nitrone **1a** and 2-phenylacetyl chloride **2a** as model substrates. As shown in Table 1, CuCl used as a catalyst only provided desired product **3aa** in 5% yield, while good yields of **3aa** were obtained using $Cu(OTf)_2$ or $Cu(NO_3)_2$ and NEt_3 as a base in THF under air (Table 1, entries 1–3).[17] The structure and relative configuration of **3aa** were further determined by X-ray diffraction analysis.[18] The yield of **3aa** was further improved to 82% when $Cu(OAc)_2$ was used as a catalyst (Table 1, entry 4). $FeCl_3$ only delivered **3aa** in 49% yield (Table 1, entry 5). Solvent screening showed that THF gave better yield than MeCN, toluene, DCM, and Et_2O (Table 1, entries 6–9). Lower yields of **3aa** were obtained using either 1.5 equiv. or 3.0 equiv. of **2a** (Table 1, entries 10 and 11). The influence of the base was also investigated. Pyridine did not afford **3aa** while tetramethylethylenediamine (TMEDA) or *N*-methylmorpholine (NMMP) delivered **3aa** in 41% and 72% yields, respectively (Table 1, entries 12–14). Therefore, the optimal conditions for preparing **3aa** were $Cu(OAc)_2$ (20 mol%), and NEt_3 (2.0 equiv.) as a base in THF from 0 °C to 25 °C under air conditions.

Table 1 Optimization of the reaction conditions[a]

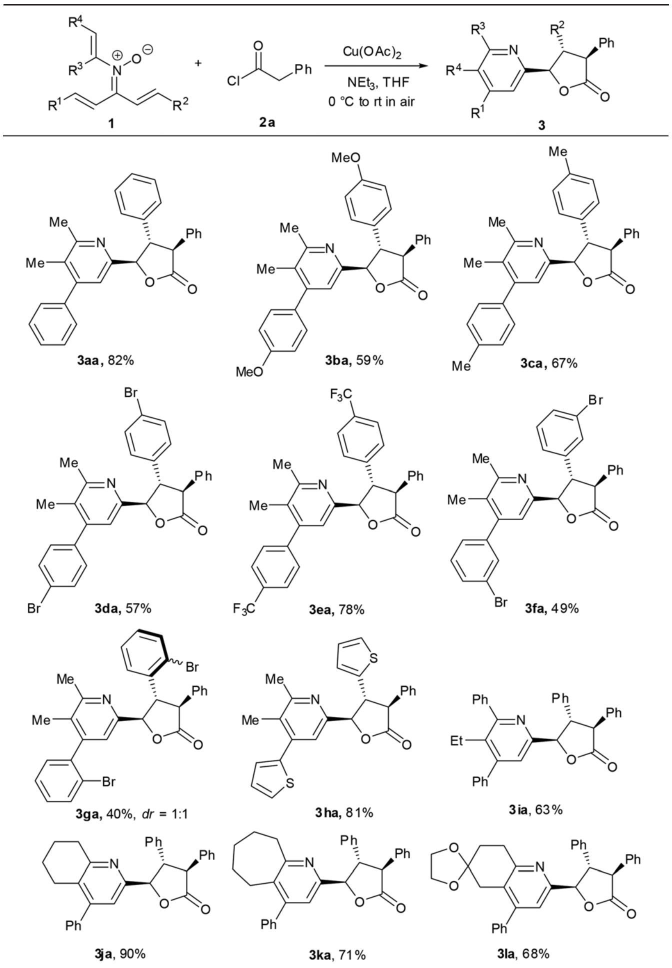


Entry	Cat.	Solvent	Base	**3aa**, yield[b] (%)
1	CuCl	THF	NEt_3	5
2	$Cu(OTf)_2$	THF	NEt_3	67
3	$Cu(NO_3)_2$	THF	NEt_3	64
4	$Cu(OAc)_2$	THF	NEt_3	82
5	$FeCl_3$	THF	NEt_3	49
6	$Cu(OAc)_2$	MeCN	NEt_3	<5
7	$Cu(OAc)_2$	Toluene	NEt_3	23
8	$Cu(OAc)_2$	DCM	NEt_3	32
9	$Cu(OAc)_2$	Et_2O	NEt_3	50
10	$Cu(OAc)_2$	THF	NEt_3	56[c]
11	$Cu(OAc)_2$	THF	NEt_3	79[d]
12	$Cu(OAc)_2$	THF	Pyridine	<5
13	$Cu(OAc)_2$	THF	TMEDA	41
14	$Cu(OAc)_2$	THF	NMMP	72

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv.), $Cu(OAc)_2$ (20 mol%), base (2.0 equiv.), solvent (3.0 mL), 0 °C to 25 °C, 24–48 h. [b] Isolated yield. [c] **2a** (1.5 equiv.). [d] **2a** (3.0 equiv.).

With the optimized conditions in hand, we turned our efforts to investigate the scope of substrates. As shown in Table 2, a variety of dibenzylidene-acetone-derived *N*-vinyl-α,β-unsaturated nitrones **1** reacting with 2-phenylacetyl chloride **2a** smoothly afforded the corresponding γ-(pyridin-2-yl) lactones **3aa–3ha** in moderate to good yields with high diastereoselectivity. The diastereoselectivity of these compounds was determined by ^1H NMR of the crude mixtures. Both electron-donating and electron-withdrawing styrenyl functional groups with *ortho*, *meta*, and *para* substituents were well tolerated to afford γ-(pyridin-2-yl)lactones **3aa–3ga**, but that with an electron-withdrawing group gave better yield than that with an electron-donating group (**3ba** *vs.* **3ea**). Interestingly, when the styrenyl group of nitrone **1g** with an *ortho*-bromo group was subjected to the optimal conditions, product **3ga** was obtained in 40% yield with a 1 : 1 dr of atropisomer. Thiophene-substituted nitrone **1h** afforded desired product **3ha** containing four heterocycles in 81% yield. In addition to the styrenyl functional groups, the *N*-vinyl substituent was varied to determine its effect on the formation of γ-(pyridin-2-yl)lactones. The R^3 and R^4 groups could be present with aryl, alkyl, and cyclic

Table 2 Substrate scope of *N*-vinyl nitrones **1** to prepare γ-(pyridin-2-yl)lactones **3**[a,b]



3aa, 82% **3ba**, 59% **3ca**, 67%

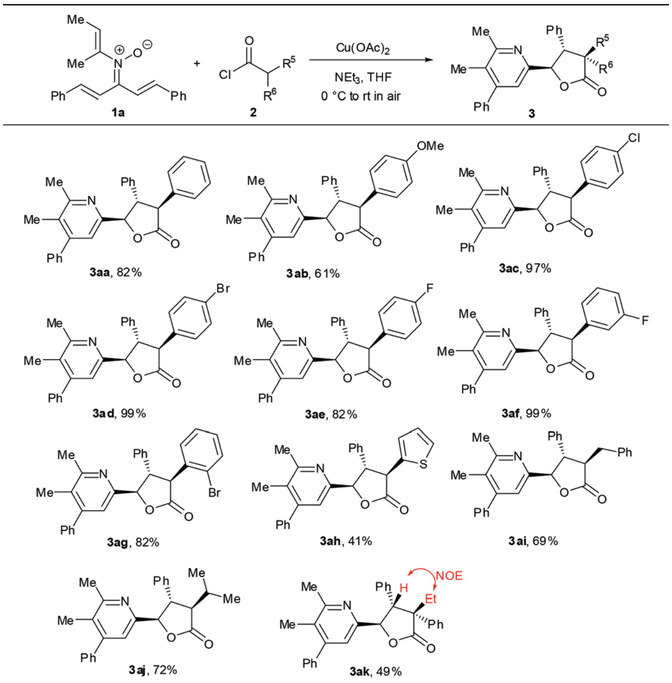
3da, 57% **3ea**, 78% **3fa**, 49%

3ga, 40%, *dr* = 1:1 **3ha**, 81% **3ia**, 63%

3ja, 90% **3ka**, 71% **3la**, 68%

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv.), $Cu(OAc)_2$ (20 mol%), NEt_3 (2.0 equiv.), THF (3.0 mL), 0 °C to 25 °C, 24–48 h. [b] Isolated yield.

Table 3 Substrate scope of acyl chlorides **2** to prepare γ-(pyridin-2-yl) lactones **3**[a,b]



3aa, 82% **3ab**, 61% **3ac**, 97%

3ad, 99% **3ae**, 82% **3af**, 99%

3ag, 82% **3ah**, 41% **3ai**, 69%

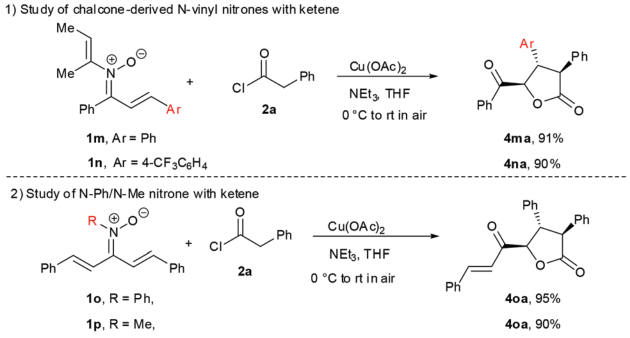
3aj, 72% **3ak**, 49%

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol, 2.0 equiv.), $Cu(OAc)_2$ (20 mol%), NEt_3 (2.0 equiv.), THF (3.0 mL), 0 °C to 25 °C, 24–48 h. [b] Isolated yield.

groups (**3ia**–**3la**). Nitrones **1j** and **1k** with six- and seven-membered rings provided products **3ja** and **3ka** in 90% and 71% yields, respectively. We were pleased to observe that nitrone **1l** with an acetal group on the six-membered ring was compatible with the reaction conditions, since this substituent further enhanced the potential synthetic utility of these compounds by simple deprotection.

Next, various acyl chlorides **2** were evaluated. As shown in Table 3, acyl chlorides with electron-donating and electron-withdrawing groups at the *ortho*, *meta*, and *para* positions afforded the desired γ-(pyridin-2-yl)lactones **3ab**–**3ak** in good to excellent yields. The R^5 and R^6 substituents of acyl chlorides tolerated aryl or heteroaryl groups, and alkyl groups. The steric hindrance of substituents in acyl chlorides had little effect on the yield of γ-(pyridin-2-yl)lactones (**3ai** *vs.* **3aj**). We are pleased to find that when the R^5 and R^6 groups of acyl chloride **2k** were Ph and Et groups, desired product **3ak** with a quaternary carbon center was obtained in 49% yield as a single isomer. Its configuration was determined by its NOESY spectrum, showing that the proton connected with the Ph group had correlations with the Et group.

The chalcone-derived *N*-vinyl-α,β-unsaturated nitrones were also tested under the standard conditions. As shown in Scheme 2, when nitrones **1m** and **1n** were subjected to the standard conditions, γ-ketolactones **4ma** and **4na** were obtained in 91% and 90% yields, respectively (Scheme 2-1). Similarly, *N*-phenyl-α,β-unsaturated nitrone **1o** and *N*-methyl-α,β-unsaturated nitrone **1p** were subjected to the optimal conditions both affording γ-ketolactone **4oa** in 95% and 90% yields, respectively (Scheme 2-2). γ-Ketolactones are one important class of heterocycles and extensively exist in biologically

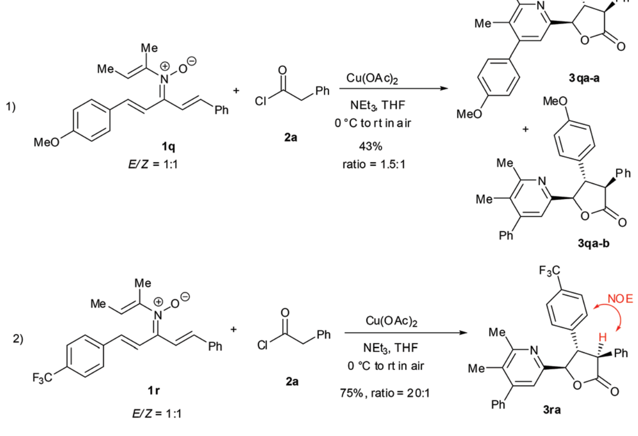


Scheme 2 Testing various chalcone-derived *N*-substituted nitrones.

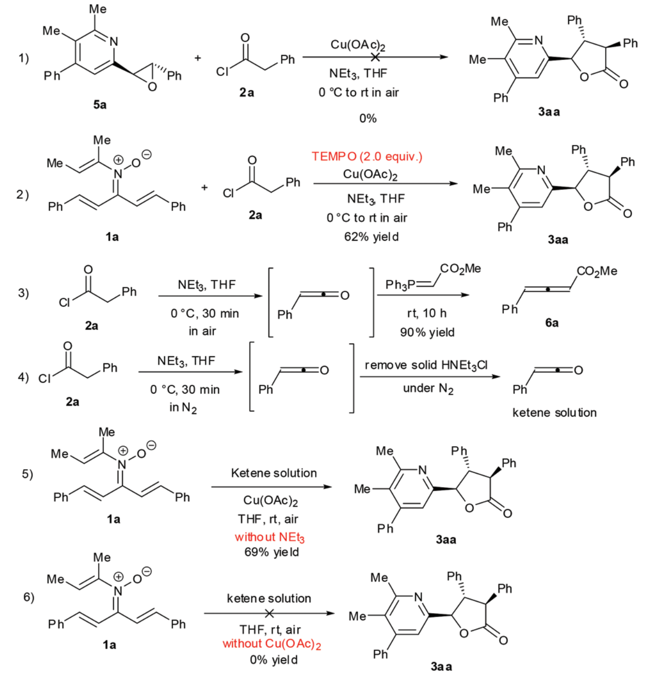
active natural products, such as phentatic acid B, cytosporanone A, and *A. strictum* lactone.[19] This method provides a good approach to prepare γ-ketolactones in excellent yields or related analogs by further reduction of γ-ketolactones from chalcone-derived *N*-substituted-α,β-unsaturated nitrones with ketenes. These results suggested that γ-ketolactone **4** was formed by hydrolysis of the imine intermediate because these substrates did not undergo 6π electron cyclization to form a pyridine ring. The results of nitrones **1o** and **1p** also indicated that the self O-transfer reaction and [3 + 2] cycloaddition can be inhibited by using ketenes and *N*-substituted-α,β-unsaturated nitrones under a copper catalyst because the epoxyketimines reported by the Anderson group[10] were not observed under these similar conditions.

We are also interested in the electronic effect on the regioselectivity of cycloaddition for unsymmetrical nitrones (Scheme 3). When a 1 : 1 *E*/*Z* mixture of nitrone **1q** with a methoxy on the styrenyl group was subjected to the standard conditions, product **3qa** was obtained in 43% yield with a 1.5 : 1 ratio (Scheme 3-1). However, a 1 : 1 *E*/*Z* mixture of nitrone **1r** with CF_3 on the styrenyl group delivered product **3ra** in 75% yield with only one isomer (Scheme 3-2). The structure of **3ra** was determined by its 2D NMR spectra. These results suggested that the styrenyl groups of nitrones with an electron-withdrawing group facilitated [5 + 2] cycloaddition and both the *E*/*Z* isomers were converted to a desired product because there are existing balance and conversion between *E* and *Z* isomers of nitrones under 20 mol% copper catalyst and 1.0 equiv. of NEt_3 at room temperature.[20]

To better understand the formation of γ-(pyridin-2-yl) lactones **3**, control experiments were performed. When epoxypyridine **5a** prepared by the self O-transfer reaction[16a] was subjected to the standard conditions, **3aa** was not observed, suggesting that epoxypyridine **5a** was not an intermediate for the formation of **3aa** (Scheme 4-1). Addition of TEMPO to the standard conditions still afforded **3aa** in 62% yield (Scheme 4-2).[21] Treatment of **2a** with NEt_3 in THF at 0 °C for 30 min, and then quenching with phosphorus ylide delivered allenoate **6a** in 90% yield (Scheme 4-3). We prepared ketene-THF solution under NEt_3 conditions by removing the produced $HNEt_3Cl$ solid (Scheme 4-4). Then, the prepared ketene-THF solution was transferred to the mixture of nitrone **1a** and $Cu(OAc)_2$ without adding NEt_3. **3aa** with a yield of 69% was obtained as only one isomer (Scheme 4-5). But no reaction occurred without adding $Cu(OAc)_2$ and only nitrone **1a** was recovered (Scheme 4-6). These results indicated that ketenes were the real reactant under the standard conditions and the copper catalyst played important roles in the simple addition and cycloaddition.

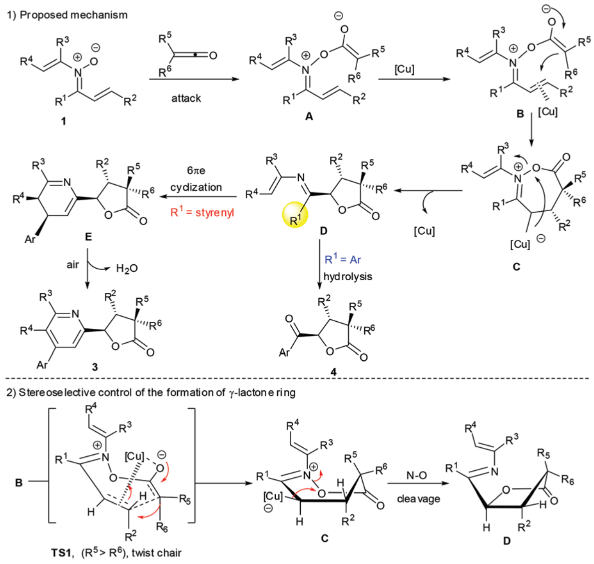


Scheme 3 Study of regioselectivity of [5 + 2] cycloaddition.

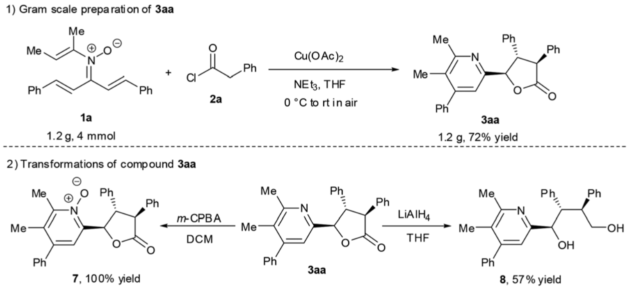


Scheme 4 Mechanistic studies.

Based on the experimental results and previous literature,[10] a plausible mechanism for the cycloaddition of nitrone **1** with acyl chloride **2** into γ-(pyridin-2-yl)lactones **3** and γ-ketolactones **4** is illustrated in Scheme 5-1. An initial addition of nitrone **1** to ketenes generated from acyl chlorides **2** under base conditions formed intermediate **A**. Coordination of the copper catalyst to the double bond of **A** gives intermediate **B**, which undergoes intramolecular addition of the generated *E*-enolate to the styrenyl groups to furnish intermediate **C**.[22,23] Then, **C** undergoes N–O bond cleavage to give intermediate **D**. When the R^1 group was a styrenyl group, **D** would undergo 6π electron cyclization to afford intermediate **E**.[24] Finally, aerobic oxidation of **E** afforded aromatic γ-(pyridin-2-yl)lactone **3**.[25] Alternatively, when the R^1 group was an aryl, hydrolysis of **D** would provide γ-ketolactone **4** due to the inhibition of 6π electron cyclization. As shown in Scheme 5-2, we assume that the high dr was obtained because of minimization of steric interactions as the attack of the generated *E*-enolate occurs *via* a twist chair transition state of a seven-membered ring (**TS1**) from **B**, which favors having R^5 and the proton at C4 on the same



Scheme 5 Proposed mechanism.



Scheme 6 The applications of compound **3aa**.

face, rather than R^5 and R^2, to afford **C**. Then, the carbanion connected with copper of **C** attacks oxygen of the N–O bond from the upside to provide **D** with high diastereoselectivity. The copper(II) catalyst likely acts as a Lewis acid to promote cyclization of the generated *E*-enolate and the N–O bond cleavage.[14c]

To demonstrate the advantages of the current approach for preparing γ-(pyridin-2-yl)lactones, a gram scale preparation of γ-(pyridin-2-yl)lactone **3aa** was performed. When 1.2 g of nitrone **1a** was reacted with **2a** under the standard conditions, 1.2 g of compound **3aa** was obtained in 72% yield (Scheme 6-1). Oxidation of **3aa** with *m*-CPBA afforded γ-(pyridin-2-yl)lactone *N*-oxide **7** in quantitative yield and reduction of **3aa** with $LiAlH_4$ afforded linear 1,4-diol **8** in 57% yield with maintenance of stereochemical integrity (Scheme 6-2), which provides an approach to access linear 1,4-diol with three chiral carbon centers.

Conclusions

In summary, we have developed a highly effective strategy to achieve copper-catalyzed [5 + 2] cycloaddition of *N*-vinyl-α,β-unsaturated nitrones with ketenes. This reaction tolerates a broad range of *N*-vinyl-α,β-unsaturated nitrones and acyl chlorides, to furnish useful and densely functionalized γ-(pyridin-2-yl)lactone structures. In addition, the reaction could also furnish γ-ketolactones in excellent yields and a privileged 1,4-diol motif through simple reduction of γ-(pyridin-2-yl) lactones. Direct and easy access to the densely functionalized γ-lactones will enable their use in biological activity studies. More importantly, we have devised a general and practical platform for the new application of the O-transfer reaction for *N*-substituted-α,β-unsaturated nitrones with ketenes and will provide a further design for other dipolarophiles in a new reaction mode.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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21 We also tested the influence of the formation of **3aa** by other radical trapping reagents under the standard conditions. The yields of **3aa** are listed as: *n*-Bu_3SnH (70%), benzoquinone (79%) and DPPH (65%).

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