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Visible-light-induced triple catalysis for a ring-opening cyanation of cyclopropyl ketones

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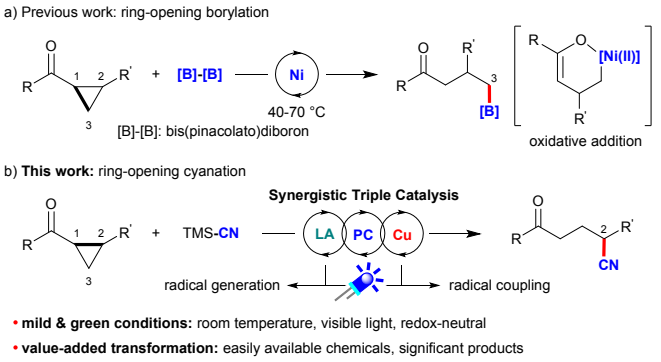
Jing Liu,[a] Xiao-Peng Liu,[a] Hong Wu,[a] Yi Wei,[a] Fu-Dong Lu,[a] Kai-Rui Guo,[a] Ying Cheng,*[a] and Wen-Jing Xiao*[a,b]

An unprecedented triple catalytic, general ring-opening cyanation reaction of cyclopropyl ketones to construct γ-cyanoketones is described. The key is to merge photoredox catalysis with Lewis acid catalysis and copper catalysis to enable the selective cleavage of carbon-carbon bond and the selective coupling of the generated radical and cyanide anion.

Multienzymatic catalysis is a powerful tool to promote a plenty of biological transformations in nature and also, it inspires synthetic chemists to develop potent multiple catalysis systems for chemical reactions in laboratory.[1] In this context, artificial multiple catalysis, also namely tandem catalysis and synergistic catalysis, with precise catalyst compatibility and reaction selectivity has been developed. However, multiple catalysis with three catalysts for radical reactions is still in its infancy.[2] Lei and co-workers developed triple metal-catalyzed radical oxidative alkynylation of terminal alkynes.[3] In addition to this triple metallic catalysis system, photoredox catalysis as an efficient approach to generate radicals under mild conditions has been introduced to triple catalyst system. In 2016, MacMillan reported an arylation of sp^3 C-H bonds of amines and cyclic ethers by the combination of photoredox, hydrogen-atom transfer (HAT) and nickel catalysis.[4a] Soon after, they extended the arylation to aldehydes[4b] and alcohols[4c] by employing this triple catalyst system. Moreover, they disclosed a direct and enantioselective α-alkylation of aldehydes with olefins catalyzed by photoredox, HAT and organocatalysis.[4d] Luo and Wu realized an asymmetric cross-dehydrogenative coupling of tertiary amines with ketones enabled by synergistic photoredox, cobalt and organocatalysis.[5] Kanai achieved dehydrogenation of *N*-heterocycles, tetrahydronaphthalenes[6a] and aliphatic alcohols[6b] by employing photoredox, HAT and transition metal (Pd, Ni) catalysis. Recently, Xu developed a dehydrogenative silylation of alkenes by combining photoredox, HAT and cobalt catalysis.[7] Though these impressive achievements, it's still highly desirable to exploit new multiple catalysis systems for accomplishing significant chemical transformations.

Cyclopropanes with exceptional reactivity are useful building blocks in chemical synthesis due to their ring strain.[8] The ring-opening reaction has been developed to transform cyclopropanes into an open-chain system. To our knowledge, the use of synergistic three catalysts system in ring-opening reaction of cyclopropanes is unknown. Encouraged by our recent work on synergistic metal- and photocatalysis,[9] we present herein the first ring-opening cyanation of cyclopropyl ketones through the combination of three different catalysts (Scheme 1b). This protocol provides a novel and general approach to synthetically valuable γ-cyanoketones[10] from readily available feedstocks under mild and green conditions. Notably, since the mechanism is distinct from traditional transition metal catalysis,[11] i.e., Ni-catalyzed ring-opening borylations of cyclopropyl ketones[11d] that proceed with a



Scheme 1 Strategies for the catalytic cleavage of C-C bonds and the ring-opening functionalization of cyclopropyl ketones. PC: photocatalyst. LA: Lewis acid.

[a]*CCNU-uOttawa Joint Research Centre, Key Laboratory of Pesticide & Chemical Biology, Ministry of Education; College of Chemistry, Central China Normal University, 152 Luoyu Road, Wuhan, Hubei 430079, China. E-mail: ycheng@mail.ccnu.edu.cn; wxiao@mail.ccnu.edu.cn. J.L. and X.P.L. contributed equally to this work.*
[c]*State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, China.*
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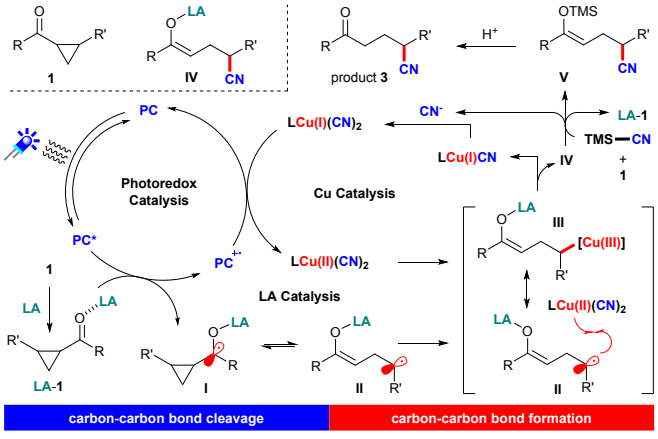
sterically sensitive oxidative addition (Scheme 1a),[11d-11e] this ring-opening cyanation shows different regio-selectivity due to the unique, photoredox-enabled single-electron transfer (SET) process.

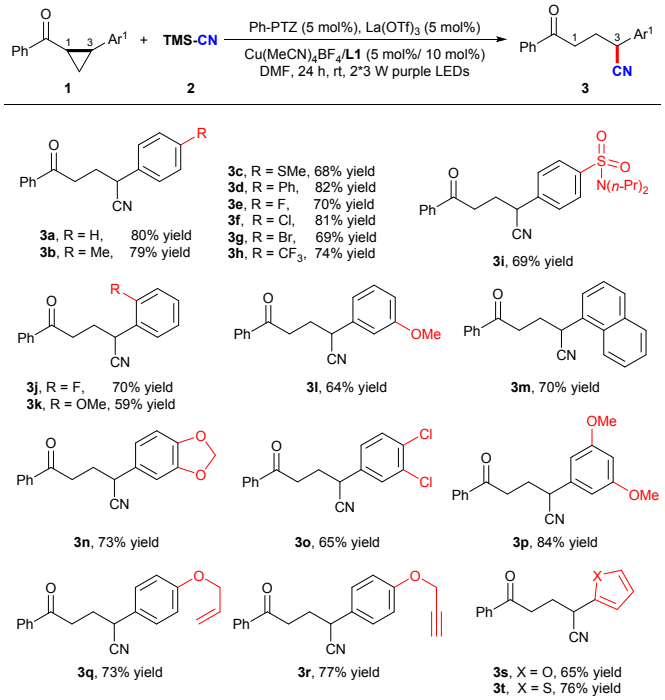
The details of the design are shown in Scheme 2. First, the excited-stated photocatalyst (PC*) would reduce the LA-activated substrate (**LA-1**) via a SET process, and generated ketyl radical anion **I** would deliver homoallylic radical **II** via a reversible ring-opening process. Next, the oxidized photocatalyst ($PC^{\cdot+}$) would be reduced to its ground state (PC) by the Cu(I) complex, $LCu(I)(CN)_2$. At the same time, the generated Cu(II) complex, $LCu(II)(CN)_2$, is expected to capture radical **II** to form Cu(III) intermediate **III**. Reductive elimination from this transient species would turn over the Cu catalysis cycle and deliver enol intermediate **IV**. Finally, silyl enol ether **V**, which can be hydrolyzed to product **3**, would be obtained from **IV** by the reaction with TMSCN, simultaneously enclosing the LA catalysis cycle and regenerating $LCu(I)(CN)_2$. For this synergistic triple catalysis, the organo-photocatalyst 10-phenyl-10H-phenothiazine (Ph-PTZ) would be highly suitable due to its capacity to harvest visible light and the strong reductive potential of its excited state (Ph-PTZ*).[12] The oxidation of $LCu(I)(CN)_2$ by $Ph\text{-}PTZ^{\cdot+}$ and the proposed radical cyanation involving the Cu(I) complex were believed to be feasible according to our previous study[9d] and Cu-catalyzed radical coupling reactions,[13] especially the Liu cyanation.[14] Although this blueprint seems efficient in principle, the LA-catalyzed addition of TMSCN to the carbonyls[15a] or the ketyl dimerization[15b] might occur competitively.



Scheme 2 Proposed ring-opening cyanation of cyclopropyl ketones. [Cu(III)] = $Cu(III)L(CN)_2$. TMSCN: trimethylsilanecarbonitrile.

To realize the above reaction, we commenced this study with phenyl(2-phenylcyclopropyl)-methanone (**1a**) as the model substrate and TMSCN (**2**) as the cyanide source (please see Table S1-5 for the details of condition optimization in Supporting Information). Based on our experience and a simple evaluation of the reaction parameters, the ring-opening cyanation of cyclopropyl ketones was successfully achieved using 5 mol% Ph-PTZ as the photocatalyst and 5 mol% $La(OTf)_3$ as the LA catalyst, together with 5 mol% $Cu(MeCN)_4BF_4$ and 5 mol% nitrogen-containing ligand **L1**, under the irradiation of purple LEDs. γ-Cyanoketone product **3a** was obtained in 80% NMR yield without cyanoalcohol and ketyl dimerization side products (Table S1, entry 1). Subsequently, a set of control experiments was performed to examine the role of each catalyst. Not surprisingly, in the absence of Ph-PTZ, $La(OTf)_3$, Cu catalyst, or light, no product was observed (Table S1, entry 2). Replacement with other Cu catalyst precursors (Table S1, entry 3), ligands (Table S1, entries 4 and 5) or LA catalysts (Table S1, entries 7 and 8) in this photoreaction resulted in lower reaction yields. A slightly increased yield was obtained by increasing the loading of ligand **L1** to 10 mol% (Table S1, entry 6: 85% yield). In addition, metal-photocatalysts were also tested. The reaction with $Ru(bpy)_3Cl_2{\cdot}6H_2O$ provided a much lower yield (Table S1, entry 9: 6% yield) and the reaction with *fac*-$Ir(ppy)_3$ provided a comparable yield (Table S1, entry 10: 77% yield).

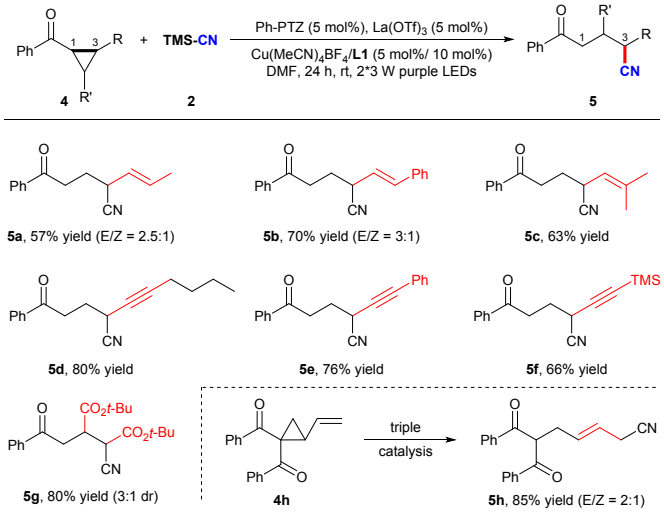
To prove the generality of this triple catalyst system, we started to evaluate the substrate scope of the ring-opening cyanations. As shown in Scheme 3, variation of the electronic properties on the aryl ring of cyclopropyl ketones **1** did not obviously affect the reaction efficiency. Both electron-donating (Me, MeS, Ph) and electron-withdrawing (F, Cl, Br, CF_3) groups were well tolerant, and provided corresponding products **3b**-**3h** in 68-82% yields. A derivative of drug molecule probenecid was a suitable substrate for this catalyst system to give new drug derivative **3i** in 69% yield. Furthermore, the effects of the position and number of substituent were also studied, and a series of γ-cyanoketone products **3j**-**3p** were delivered in 59-84% yields. In addition, substrates bearing functionalized aryl groups (i.e., allyl and propargyl) and heteroaryl motif (i.e.,



Scheme 3 Variation of the aryl substituents in the cyclopropyl ketones. Reaction conditions: as indicated in entry 6 in Table S1; isolated yield based on **1**.

furan and thiophene) were effective in this transformation, producing γ-cyanoketone products **3q**-**3t** in 65-77% yields.

Given the synthetic versatility of alkenes and alkynes, we further examined the cyclopropyl ketones having these functional groups under the optimal conditions. As illustrated in Scheme 4, a variety of alkenyl groups with an alkyl (**5a**) or aryl substituent (**5b**), or having two alkyl substituents (**5c**) were proven to be compatible, affording the different γ-cyanoketones in 57-70% yields. The reaction of cyclopropyl ketones with an alkyl alkyne (**4d**), aryl alkyne (**4e**) and TMS-substituted alkyne (**4f**) also proceeded well and afforded the desired products in 66-80% yields.[16] Moreover, this protocol can be successfully extended to substrates with ester functional groups. For example, when two esters were introduced to the substrate, the reaction can proceed smoothly and produce highly functionalized product **5g** in a good yield. When vinylcyclopropane substrate **4h** was subjected to the triple catalyst system, the reaction occurred and afforded the cyanation product **5h** with an unexpected terminal selectivity. At current stage, alkyl-substituted substrates were ineffective under the optimal conditions might due to the low ring opening rate.[17]

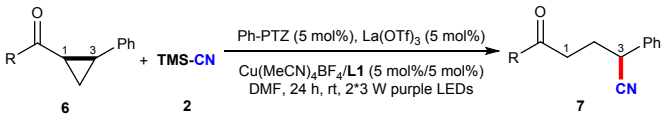


Scheme 4 Introducing other substituents in the cyclopropyl ketones. Reaction conditions: as indicated in entry 6 in Table S1; isolated yield based on **4**.

Next, we investigated the substrate generality with respect to the aryl ketone component (Table 1). The substitution pattern and electronic properties of the aryl ring did not obviously affect the reaction efficiency and a series of γ-cyanoketones **7a**-**7g** possessing F, Cl, Br, Me or MeO groups were produced in 72-90% yields (Table 1, entries 1-7). 2-Naphthyl-substituted substrate **6h** also reacted well with TMSCN to afford corresponding product **7h** in 75% yield (Table 1, entry 8). Moreover, a cyclopropyl ketone bearing a heteroaryl substituent, *N*-methyl imidazole, was well tolerated and provided the desired product **7i** in 89% yield (Table 1, entry 9). Notably, sequential operations to this product, namely a methylation followed by a nucleophilic substitution by benzyl Grignard reagent or methanol, afforded alkyl-substituted γ-cyanoketone **8** or γ-cyanoester **9** (Scheme 5a).

This procedure represents an important complement to the current limitation that aryl or heteroaryl ketones are necessary for the photochemical reductions.[18]

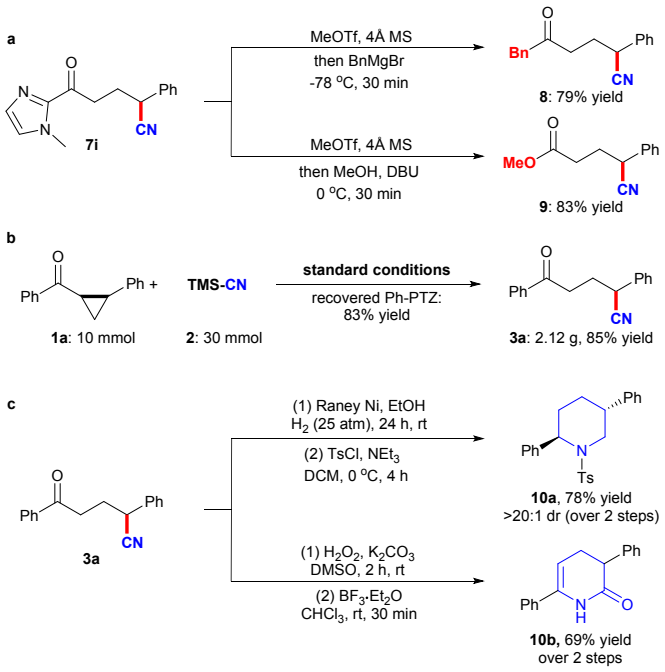
Table 1 Variation of the acyl group in the cyclopropyl ketones[a]



Entry	Substrate **6**	Product **7**	Yield (%)[b]
1	**6a:** R = 4-F-C_6H_4	**7a**	90
2	**6b:** R = 4-Cl-C_6H_4	**7b**	79
3	**6c:** R = 4-Me-C_6H_4	**7c**	88
4	**6d:** R = 4-OMe-C_6H_4	**7d**	85
5	**6e:** R = 2-OMe-C_6H_4	**7e**	89
6	**6f:** R = 3-Br-C_6H_4	**7f**	72
7	**6g:** R = 3,4-MeO-C_6H_3	**7g**	89
8	**6h:** R = 2-Naphthyl	**7h**	75
9	**6i:** R = *N*-methylimidazole	**7i**	89

[a] Standard conditions as indicated in entry 6 of Table S1. [b] Isolated yield.

To further demonstrate the utility of this methodology, a gram-scale reaction of model substrate **1a** was conducted using the synergistic triple catalyst system. As highlighted in Scheme 5b, 2.12 g of product **3a** was obtained without erosion of the reaction efficiency. Notably, 83% yield of the organo-photocatalyst, Ph-PTZ, can be recovered. Additionally, synthetic transformations of γ-cyanoketone **3a** were carried



Scheme 5 Synthetic utility of methodology. **a** Synthesis of γ-cyano ketone and ester. **b** Gram-scale experiment. **c** Aza-heterocycle synthesis from **3a**.

out to generate a piperidine skeleton, which is an important aza-heterocyclic moiety in alkaloids, pharmaceuticals and agrochemicals.[19] For example, a reductive cyclization promoted by Raney Ni under a H_2 atmosphere followed by protection can afforded piperidine product 1**0a** in 78% yield (Scheme 5c, up); complete hydrolysis of the nitrile to the amide followed by a BF_3-promoted intramolecular condensation gave the dihydropyridin-2(1H)-one product **10b** in 69% yield (Scheme 5c, bottom).

In summary, a synergistic triple catalyst system has been developed for the ring-opening cyanation of cyclopropyl ketones. The combination of organo-photoredox catalysis with Lewis acid catalysis and copper catalysis enables the selective cleavage of carbon-carbon bonds and radical cyanation. This protocol provided a series of γ-cyanoketones in good yields in an eco-friendly and sustainable manner. The synthetic utility of the methodology has been demonstrated through the construction of significant piperidine moieties. It is anticipated that synergistic triple catalysis strategy developed in this study will have broad applications in the development of new catalytic ring-opening transformations of strained systems.

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Graphic abstract for

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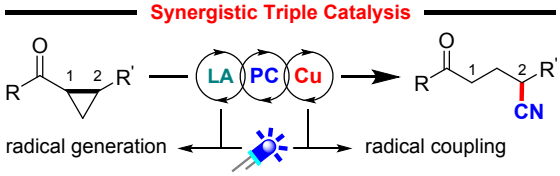

Ring-Opening Cyanation: 37 examples, up to 90% yield

A ring-opening cyanation of cyclopropyl ketones was developed via a synergistic triple catalysis strategy, providing a wide range of γ-cyanoketones in good reaction efficiencies under mild and eco-friendly conditions.