

# Photo/N-Heterocyclic Carbene Co-catalyzed Ring Opening and $\gamma$ -Alkylation of Cyclopropane Enal

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s they are the fundamental structures of organic Compounds, the formation, cleavage, and transformation of C-H and C-C bonds are of pivotal importance in synthetic chemistry. Compared to the widely explored C-H functionalization,  $^{1}$  C–C activation, which edits the molecular framework, is still very limited.<sup>2</sup> The ring opening of cyclopropane provides an efficient strategy for C-C bond cleavage because of the release of ring strain.<sup>3</sup> For example, the ring opening of donor-acceptor cyclopropane catalyzed by Lewis acid has been well developed.<sup>4</sup> However, the reaction usually goes well with heteroatom nucleophiles or enolates, while the reaction with a  $C(sp^3)$  nucleophile is still a challenge (Scheme 1a).<sup>3</sup> The C-C bond cleavage of cyclopropane by transition metal catalysis and the following reactions with alkenes/alkynes were also developed (Scheme 1b).<sup>6</sup> Interestingly, the reaction with electrophiles via the C-C bond cleavage of cyclopropane has rarely been reported.

In the past few decades, organocatalysis of N-heterocyclic carbenes (NHCs) has emerged as a useful strategy for the umpolung of various substrates.<sup>7</sup> The NHC-catalyzed redox esterification of formylcyclopropanes via C-C bond cleavage was pioneered by Bode et al. in 2006.8 The corresponding reactions of the enolate/dienolate9 with carbonyl compounds,<sup>10</sup> fluorinated reagents,<sup>11</sup> and azodicarboxylate esters<sup>11</sup> have also been established via a two-electron pathway (Scheme 1c). However, NHC-catalyzed C-C bond cleavage with  $C(sp^3)$  electrophiles is still undocumented. As a continuation of our efforts in merging photoredox catalysis<sup>12</sup> with NHC catalysis,<sup>13</sup> we envision that the highly reactive alkyl radical, generated under photocatalysis, may react with the dienolate generated from cyclopropane enal via NHC-catalyzed ring opening, which features C-C bond activation under organocatalysis and reaction with  $C(sp^3)$  electrophiles (Scheme 1d).

Our investigation commenced with the reaction of cyclopropane enal **1a** and diethyl 2-bromo-2-methylmalonate **2a** in the presence of methanol under photo/NHC catalysis (Table 1). Despite the fact that there is no desired ring-opening alkylation product 3a observed for the reaction using thiozolium A as the NHC precursor and 2 mol %  $Ru(bpy)_3(PF_6)_2$  as the photocatalyst under blue light-emitting diode (LED) irraditation (entry 1), It was found that the corresponding reactions using imidazolium preNHC B and triazolium preNHC C1 and C2 gave product 3a in 5-11% yields with exclusive  $\gamma$ -regioselectivity (entries 2–4, respectively). The triazolium preNHC C3 and C4 with an Nelectron-deficient aryl group failed to catalyze the reaction (entries 5 and 6, respectively). Gratifyingly, the use of tetracylic trizaolium preNHC D dramatically improved the yield of the reaction to 83% with exclusive  $\gamma$ -regioselectivity (entry 7). Decreasing the load of the photocatalyst to 1 mol % led to decreased yields (entries 8 and 9), while a better yield resulted with 2.5 mol % photocatalyst (entry 10). Finally, the yield was maintained when the load of preNHC D was decreased to 10 mol %. (entry 11).

After optimization of the reaction conditions, the scope of alcohols for the reaction was then briefly explored (Scheme 2). It was found that all of the primary alcohols with electrondonating or electron-withdrawing groups worked well for the reaction, furnishing the corresponding cross coupling products (3a-3d) in good to excellent yields. Moderate to good yields were also achieved for the reaction with secondary alcohols when its load was increased (3e and 3f). It is noteworthy that chloride and olefin were tolerated to furnish the desired products (3g and 3h) in good to excellent yields. Furthermore, the reaction could be scaled up with 3 mmol of 2a, giving 1.15 g of the corresponding ring-opening alkylation product 3a in 87% yield.

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# Scheme 1. C-C Bond Cleavage of Cyclopropanes

a) Lewis acid-catalyzed reaction with nucleophiles







[M] = organometallic catalysts

c) NHC-catalyzed reaction via two electron pathway







<sup>*a*</sup>General conditions: **1a** (0.75 mmol), **2a** (0.30 mmol), Ru-(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> (1–2.5 mol %), preNHCs (10–20 mol %), CsOAc (200 mol %), MeOH (5.0 equiv), DCE (3 mL),  $18 \times 1$  W household blue LED, 12 h, 25 °C. <sup>*b*</sup>Isolated yields.

# Scheme 2. Substrate Scope of Nucleophiles



<sup>b</sup> 20 equiv. of R'OH was used.

#### Scheme 3. Substrate Scope of Alkyl Electrophiles



# Scheme 4. Chemical Transformations







A variety of brominated compounds were then explored as the radical precursors (Scheme 3). It was found that a series of pubs.acs.org/OrgLett

# Scheme 6. Preliminary Mechanistic Studies



 $\alpha$ -alkyl- $\alpha$ -bromomalonates bearing linear and branched aliphatic chains worked well to afford the corresponding products (3i-3k) in good yields with exclusive  $\gamma$ -regioselectivity. The reaction with  $\alpha$ -benzyl- $\alpha$ -bromomalonate with electron-donating and electron-withdrawing groups went smoothly, giving the corresponding products 31-30 in good to excellent yields. The aryl group with an ortho substituent, a meta substituent, or a  $\beta$ -naphthyl did not affect the reaction (3p-3r). More importantly, the brominated compounds with additional functional groups, such as boronic ester, olefin, and  $\alpha,\beta$ -unsaturated ester, were all well tolerated (3s-3u). Interestingly, the reaction with methyl 2-(bromomethyl)-5nitrobenzoate afforded the product in reasonable yield (3v). Furthermore, a simple alkylation reagent,  $\alpha$ -iodoacetonitrile, worked well to give the product in 64% yield (3w). Unfortunately, 2-bromo-2-nitropropane did not work under our current reaction conditions (3x). Attempts to expand the scope of the enals, such as epoxy enals and several other cyclopropane enals, failed to give desired products under the current conditions (see the Supporting Information for details).

The multifunctional ring-opening alkylation product allows many possible further derivations. For instance, hydrogenation of malonate derivative **3a** with  $Pd(OH)_2/C$  under  $H_2$  provided product **4a** in 91% yield. Bromination of compound **3a** by NBS afforded the corresponding  $\alpha$ -bromo malonate **4b** in 71% yield (Scheme 4).

A promising enantioselectivity was achieved when chiral NHC precursor E was used for the reaction (Scheme 5).

A series of control experiments were conducted to illustrate the reaction mechanism (Scheme 6). The reaction without light, photocatalyst, or NHC afforded no desired product. The reaction was completely prohibited when TEMPO was added as the radical scavenger, while radical coupling adduct **5a** of the  $\alpha$ -methylmalonate radical and TEMPO was detected by highresolution mass spectrometry.

A plausible mechanism for the reaction is shown in Scheme 7. Alkyl radical I is generated from alkyl halide via photoredox catalysis. Radical I reacts with dienolate intermediate II, which is generated from  $\gamma$ -cyclopropane enals via NHC-catalyzed C–C bond cleavage, to give homoenolate radical III. The subsequent single-electron transfer oxidation of homoenolate radical III by Ru<sup>III</sup> photocatalyst IV furnishes unsaturated acyl azolium intermediate V and completes the photoredox catalytic cycle. Acyl azolium intermediate V is trapped by alcohol to give the final  $\gamma$ -alkylated  $\alpha,\beta$ -unsaturated ester and regenerates the NHC catalyst.

In summary, an unprecedented NHC-catalyzed C–C bond cleavage of  $\gamma$ -cyclopropane enals and the following  $\gamma$ -alkylation via radicals under photoredox conditions were developed. A variety of halogenated alkylation reagents, such as  $\alpha$ -alkyl- $\alpha$ bromomalonates, methyl 2-(bromomethyl)-5-nitrobenzoate, and iodoacetonitrile, worked well for the reaction, providing the desired  $\gamma$ -alkylated  $\alpha$ , $\beta$ -unsaturated esters in moderate to good yields. The reaction features exclusive  $\gamma$ -regioselectivity, tolerance of functional groups, and mild reaction conditions. Further investigation of NHC/photo-co-catalyzed reactions is underway in our laboratory.





### ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04533.

Experimental procedures, full spectroscopic data for all new compounds, and copies of <sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR spectra (PDF)

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# Notes

The authors declare no competing financial interest.

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