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Letter

# Vinylboron Self-Promoted Carbonylative Coupling with Cyclobutanone Oxime Esters

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**(5)** Supporting Information

**ABSTRACT:** Despite the significant progress that has been made in the area of catalyst-dependent chemistry, the exploration of a greener and more environmentally benign catalyst-free reaction remains one of the most important areas in modern chemistry. Herein, we present a vinylboron self-promoted carbonylative coupling with cyclobutanone oxime esters. Various cyclobutanone oxime esters and



substituted styrylboronic acids can be transformed into the corresponding enones in moderate to good yields. Detailed EPR investigations and control experiments provide sufficient evidence to show that this reaction goes through a single-electron transfer process.

ver the past decades, the concept of green chemistry has aroused a greater awareness and interest in academic and industry researchers since it meets environmental and economic goals.<sup>1</sup> Impressive progress has been achieved in various research areas, such as the exploration for a greener and more sustainable process, and the design of safer chemicals and environmentally friendly feedstocks. Recently, investigations into catalyst-free reactions<sup>2</sup> have attracted broad attention among chemists as well. In general, the catalyst is a crucial factor for a reaction, which can promote faster chemical reactions, and better selectivity also can be obtained by using special catalysts or reagents. Although avoiding the use of a catalyst is a highly challenging task, many elegant works were established by different groups since the earliest example of cycloaddition reaction between furan and maleic anhydride in water without any catalyst was reported in 1931.<sup>3</sup>

On the other hand, carbonylation reactions are widely used in both large and small scales for the production of fine and bulk chemicals, which provide an efficient method for introducing a synthetically useful carbonyl group into their parent molecules. Recently, our group disclosed a series of nitrogen-centered radicals mediated carbonylation reactions. These nitrogen radicals were generated from the transitionmetal-catalyzed cleavage of N-halogen bonds and then captured by CO gas to give the corresponding carbonylcontaining products.<sup>4</sup> Besides, cyclobutanone oxime esters as a good precursor for generating an iminyl radical received considerable attention over the years. Different kinds of transition metals, such as rhodium,<sup>5</sup> palladium,<sup>6</sup> nickel,<sup>7</sup> iron,<sup>8</sup> copper,<sup>9</sup> and photocatalysts,<sup>10</sup> have been successfully used for the activation of these compounds (Scheme 1). However, the direct carbonylative coupling of cyclobutanone oxime esters in the absence of catalyst or light remains unknown in literature.<sup>11</sup>

Based on these backgrounds, we turned our attention toward exploring the possibility of a catalyst-free carbonylation reaction. Initially, cyclobutanone *O*-benzoyl oxime and *trans*- Scheme 1. Methodologies for the Coupling of Cyclobutanone Oxime Esters with Styrylboronic Acids

O Previous methods for the coupling of cyclobutone oxime esters with styrylboronic acid



styrylboronic acid were selected as the model substrates to test our hypotheses. To our delight, after screening various reaction conditions, we found that the best results can be obtained in DMAc/H<sub>2</sub>O (10:1) at 120 °C under 50 bar of CO in the absence of any additional catalyst, which produced the desired  $\alpha,\beta$ -unsaturated ketone in 61% isolated yield (for details on optimization of the reaction conditions; see Supporting Information).

To gain deeper knowledge regarding the reaction mechanism, the reaction between **1a** and **2a** was investigated by in situ electron paramagnetic resonance (EPR) in the presence and absence of 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) as a spin trap to detect the short-lived radicals which might be formed during the course of the reaction. In the absence of DMPO, the EPR spectrum of the reaction mixture containing **1a** and **2a** in CH<sub>3</sub>CN at 77 °C shows no signal even after heating the solution for 30 min. However, in the presence of DMPO, the EPR spectrum shows a six-line signal at g = 2.007 with AN = 13.6 G and  $A\beta$ H = 19.6 G (Figure 1) characteristic of a DMPO-R spin adduct. A similar EPR signal was observed when only **2a** was heated at 77 °C in CH<sub>3</sub>CN in the presence of DMPO suggesting that the catalytic reaction might be initiated by the formation of a new radical from **2a**. Then the

Received: January 26, 2019



Figure 1. EPR spectra before (black line) and after addition of DMPO to reaction EPR 1 measured at 20  $^{\circ}$ C after heating the mixture at 77  $^{\circ}$ C for 30 min.

reaction of the new radical with 1a leads to generation of an iminyl radical intermediate which is also a carbon-centered radical. For this reason, we cannot distinguish the radical type between 2a and EPR 1 reaction by EPR since both of them lead to the formation of DMPO-R spin adducts.

Furthermore, several control experiments were conducted to further understand the reaction mechanism. As shown in Scheme 2, styrene was used to replace the *trans*-styrylboronic acid **2a** as substrates, and a 20 mol % boron source including PhB(OH)<sub>2</sub>, bis(pinacolato)diboron ((Bpin)<sub>2</sub>), BF<sub>3</sub>·Et<sub>2</sub>O, and **2a** were added into reaction mixtures as the catalyst. However, no desired product **3a** was detected in these control





experiments  $\mathbf{a}-\mathbf{c}$ , and only an 8% GC yield was obtained in the control experiment **d**. Then the reaction was conducted with 1.5 equiv of TEMPO under standard conditions, which completely inhibited the reaction to form product 3**a**. The alkylated TEMPO product was formed in 54% isolated yield. Finally, (*E*)-(2-(4-chlorostyryl)-4,5,5-trimethyl-1,3,2-dioxaborolan-4-yl)methylium 2**h** was selected to react with 1**a** under the standard conditions. This reaction proceeded smoothly and gave the corresponding product 3**d** in 35% isolated yield. Moreover, (*E*)-6-phenylhex-5-enenitrile can be obtained in the absence of carbon monoxide (Scheme 2g).

Based on the results of control experiments and EPR results, we proposed a possible reaction mechanism, shown in Scheme 3. Initially, promoted by **2a** and DMAc, an iminyl radical **A** was

#### Scheme 3. Proposed Mechanism



generated from 1a. Subsequently, the iminyl radical A goes through a ring-opening process to produce a highly reactive cyanoalkyl radical B, which will be trapped by CO to give intermediate C. Addition of the acyl radical C to *trans*styrylboronic acid forms a new benzyl radical D. Finally, intermediate D will be transformed into the desired  $\alpha_{,\beta}$ unsaturated ketone 3a after reaction with substrate 1a.

With the optimized reaction conditions in hand, we next evaluated the substrate scope of this reaction with a range of cyclobutanone oxime esters and (E)-styrylboronic acid derivatives. As shown in Table 1, various substituted styrylboronic acids worked well under the standard conditions. Electron-withdrawing groups such as fluorine, chloride, and trifluoromethyl at the para position of the aromatic ring led to the corresponding  $\alpha_{\beta}$ -unsaturated ketones in moderate yields (Table 1, 3b-3d). In addition, electron-donating groups at the para position also proceed smoothly under the standard conditions and deliver the desired products in moderate to good yield (Table 1, 3e-3g). The substrate bearing a para methyl group gives the ketone product in 75% yield (Table 1, 3f). However, in the cases of  $\alpha$ -vinylboron and alkyl vinylboron such as (1-phenylvinyl)boronic acid and (E)-(2cyclohexylvinyl)boronic acid, no desired product could be detected and substrates decomposed. Subsequently, cyclobutanone oxime esters with various functional groups including phenyl, benzyl, octanoyl, and ester were tested and the corresponding products were obtained in moderate yields (Table 1, 3h-3k). Disubstituted cyclobutanone oxime ester also engaged in this reaction smoothly, leading to the desired products in 45% and 47% yields respectively (Table 1, 3l, 3m). It should be noted that the Boc-protected piperidine derivative showed comparable reactivity and formed the desired  $\alpha_{\beta}$ unsaturated ketone in 40% yield (Table 1, 3n). Finally, nonsymmetrical cyclobutanone oxime ester derivatives delivered the corresponding  $\alpha_{\beta}$ -unsaturated ketones in 33% and

# Table 1. Scope of Vinylboron Self-Catalyzed Carbonylation<sup>a</sup>



<sup>&</sup>lt;sup>*a*</sup>Reaction conditions: **1a** (0.20 mmol, 1.0 equiv), **2a** (0.24 mmol, 1.2 equiv) in 3.3 mL of DMAc/H<sub>2</sub>O (10:1) at 120  $^{\circ}$ C for 20 h, under 50

#### Table 1. continued

bar of CO; isolated yields. <sup>b</sup>1 mmol scale: **1a** (1 mmol, 1.0 equiv), **2a** (1.2 mmol, 1.2 equiv) in 5.5 mL of DMAc/H<sub>2</sub>O (10:1) at 120 °C for 20 h, under 50 bar of CO; isolated yields.

20% yields, in which C–C bond cleavage occurred selectively at the more hindered position (Table 1, 30, 3p). However, no desired product could be detected when cyclopentanone or cyclohexanone oxime esters were tested with styrylboronic acid under our standard conditions.

In summary, a new method for the synthesis of diverse cyano-containing  $\alpha_{,\beta}$ -unsaturated ketone products has been established. The reaction was conducted in DMAc/H<sub>2</sub>O in the absence of any additional catalyst. Various cyclobutanone oxime esters and substituted styrylboronic acids can be converted into the corresponding products in moderate to good yields. In addition, EPR investigations and control experiments also clearly showed that this reaction goes through a single-electron transfer pathway.

#### ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b00333.

General comments, general procedure, optimization details, analytic data and NMR spectra (PDF)

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### Notes

The authors declare no competing financial interest.

#### ACKNOWLEDGMENTS

We thank the analytical department of Leibniz-Institute for Catalysis at the University of Rostock for their excellent analytical service. We also appreciate the general support from Professor Armin Börner and Professor Matthias Beller in LIKAT.

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