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Letter

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ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.8b03576 • Publication Date (Web): 24 Oct 2018

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Gallic Acid-Promoted SET Process for Cyclobutanone Oximes Activation and (Carbonylative-)Alkylation of Olefins

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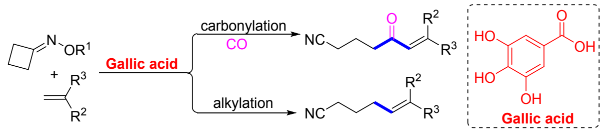
Keywords: gallic acid; cyclobutanone oximes; carbonylation; carbonylative coupling; radical process; domino reaction

Supporting Information Placeholder

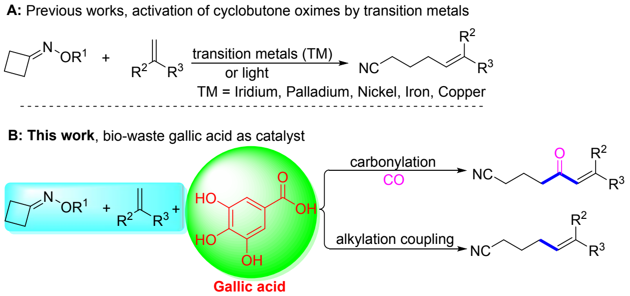
ABSTRACT: Despite the general success of metal catalysts in modern organic chemistry, the exploration of natural available organic molecules as catalysts still have a strong appeal to scientists due to their green and sustainable advantages. Herein an intermolecular coupling reaction of cyclobutanone oximes with olefins promoted by bio-waste gallic acid is reported. Both alkylation and carbonylative alkylation reactions proceeded well in this system. Various cyclobutanone oximes and olefins can be transformed into the corresponding products in moderate to good yields. Detailed EPR investigations and control experiments are consistent with a single-electron transfer mechanism.



Organic radicals are one of the most important reactive intermediates in modern organic chemistry. Although their chaotic and uncontrollable properties, many useful and elegant radical reactions have been developed and used in organic synthesis and even industry processes over the past decades.[1] Free radicals may be generated in a number of ways, typical methods involve electrolytic, photolytic, borane oxidative homolytic, and organo-tin hydride systems, are known to produce various kinds of radicals. In the past decade, considerable research efforts have been devoted to the development of photo-redox catalysis radical reactions.[2] However, the photosensors are still relatively expensive, and transition-metal catalysts are usually needed in the other cases (Scheme 1). There are still fairly few studies concerning organic molecules catalyzed free radical chemistry.

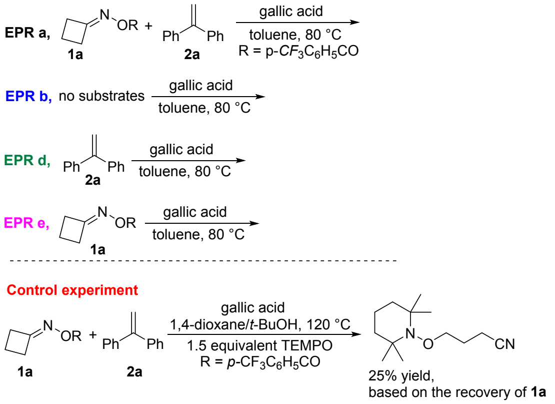
On the other hand, sustainable and renewable processes with the use of natural 'feedstocks' in chemical synthesis as an alternative to hazardous chemical reagents or expensive metal-based catalysts are important to our environment. Particularly, the reutilization and valorization of the numerous residues generated by agricultural activities are attractive.[3] Gallic acid is an inexpensive antioxidant and commonly used as a food additive, which is present in a considerable amount in bio-wastes such as grape pomace or oak bark.[4] According to the concept of sustainable and renewable process, gallic acid seems to fit perfectly well. Additionally, gallic acid has been applied as catalyst in some studies, such as, reduce arenediazonium ions to aryl radical,[5] hydration of alkynes under mild conditions[6] and convert atmospheric oxygen into hydrogen peroxide and oxidize arylboronic acids to the corresponding phenol products.[7] Therefore, we become interested to explore a sustainable radical (carbonylation-)reaction with gallic acid as the promotor.

Cyclobutanone oximes and their derivatives are very useful intermediates in organic synthesis. Considerable attentions have been attracted to the selective functionalizations via C-C bond cleavage over the years. Various transition-metals, like rhodium,[8] iridium,[9] palladium,[10] nickel,[11] iron,[12] and copper[13] complexes, have been successfully used for the activation of C-C bonds in these compounds. Very recently, photocatalytic systems for the C-C bonds activation of cyclobutanone oximes have been achieved as well.[14] Herein, we developed the first gallic acid-catalyzed (carbonylation-)alkylation reaction of cyclobutanone oximes with olefins. The best results can be obtained in the presence of 10-20% equivalent of gallic acid in 1,4-dioxane/*t*-BuOH (1:1) at 120 °C for 20 hours, which gave the desired product **3a** and **4a** in 78% and 89% isolated yields, respectively. (Details on optimization of the reaction conditions see Supporting Information (ESI)).



Scheme 1. Methods for cyclobutanone oximes activation.

To gain some deeper insights into the reaction mechanism, reactions between gallic acid, cyclobutanone oximes **1a** and 1,1-diphenylethylene **2a** in toluene was investigated by in-situ 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 reaction. In the absence of DMPO, the EPR measurement of the reaction mixture (containing **1a**, **2a**, and gallic acid in toluene at 80 °C) shows only very weak signal at g = 2.004 without hyperfine structure due to the formation of organic radical (Scheme 2). However, in the presence of DMPO, the EPR spectrum is very complex due to superimpose of several EPR signals arising from different spin adducts (Figure 1). To figure out the origin of these species and to prove that the catalytic reaction process is initiated by the gallic acid the reactions between gallic acid and substrates **1a** and **2a** were investigated separately by in-situ EPR in the presence of DMPO. EPR spectrum of gallic acid suspension in toluene (at 80 °C) shows a six-line signal at g = 2.007 with coupling constant A_N = 13.5 G and $A_{\beta H}$ = 10.9 G due to the formation of DMPO-OR spin adduct suggesting that the catalytic reaction proceeded through a radical pathway. Addition of substrate **2a** to the gallic acid does not significantly change the EPR signal features, which indicates that **2a** reacts very slowly with gallic acid. However, addition of substrate **1a** to gallic acid results appearing of new signal at g = 2.007 with A_N = 13.6 G and $A_{\beta H}$ = 18.9 G due to the formation of DMPO-R spin adduct suggesting that one electron is transferred from gallic acid to the cyclobutanone oximes **1a** is more pronounced than to substrate **2a**, which then generates the iminyl radical (intermediate **A** in scheme 3, i.e carbon centered radical). Reaction of **1a** with **2b** results in the formation of **C** radical intermediate. This reason why the EPR spectrum of the reaction mixture is very complex, i.e due to the formation of at least three radical species namely gallic acid, **B** and **C** radicals. These experiments provided definitive proof for the reaction begin from the **1a** and gallic acid. In addition, the reaction with 1.5 equivalents of TEMPO completely inhibited the reaction to form product, and the alkylated TEMPO product was formed in 25% yield based on the recovery of **1a**. This result also suggested the existence of radical species in this reaction. It is also important to mention that our model systems were performed in dark as well and the same range of yields were obtained. However, only small amount of the desired products could be detected in the absence of gallic acid, even the control reactions were ran for three days.



Scheme 2. EPR investigations and control experiments.

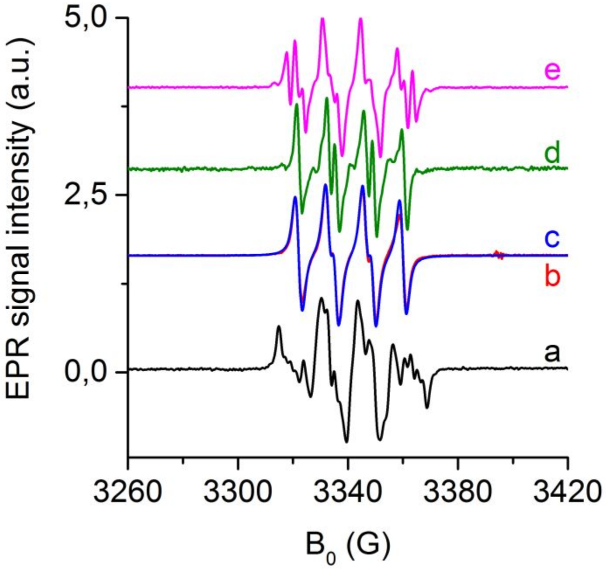
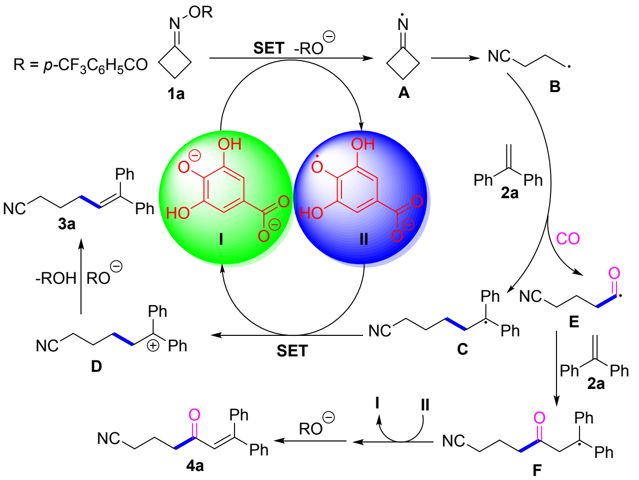


Figure 1. EPR spectra after addition of DMPO at 80 °C to a) reaction a; b) reaction b; c) simulated spectrum of (b); d) reaction d; e) reaction e.

Based on these results and literatures,[5-7] a possible reaction mechanism is proposed and shown in Scheme 3. The reaction begins with the gallate ion **I** induced SET reduction of cyclobutanone oximes **1a** to give the iminyl radical **A** and galloyl radical **II**. It is known that the radical at 4-OH in the galloyl radical is stabilized by two hydrogen bond interactions and by the captodative effect.[15] Then, the iminyl radical **A** undergoes a ring-opening by homolytic C-C single bond cleavage to produce a highly reactive cyanoalkyl radical **B**. Addition of **B** to 1,1-diphenyl ethylene **2a** forms carbon radical **C**, which is more stabilized and relatively less reactive. Subsequently, the gallate ion **I** is regenerated by means of the single electron oxidation of radical **C** to carbocation intermediate **D**. Finally, **D** undergoes a facile base-mediated deprotonation to provide the alkene product **3a**. While in the presence of carbon monoxide, cyanoalkyl radical **B** will be trapped by CO in advance of the reaction with 1,1-diphenyl ethylene **2a** to give intermediate **F** via intermediate **E**. Under the assistance of catalyst, intermediate **F** will be transformed into the desired carbonylation product **4a**.

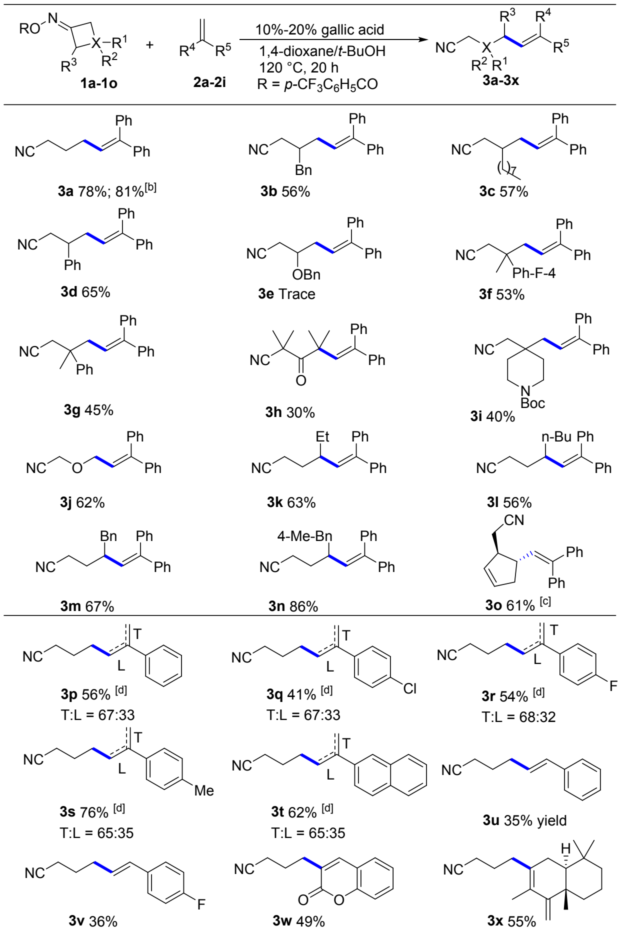


Scheme 3. Proposed mechanism.

With the optimized reaction conditions in hand, we next evaluated the substrate scope of this reaction with a range of cyclobutanone oximes and olefins. As shown in Table 1, symmetrical cyclobutanone oximes with different kinds of functional groups including phenyl, benzyl, and octanoyl can be transferred into the corresponding products in moderate yields (Table 1, **3b-3d**). Di-substituted cyclobutanone oximes (Table 1, **1f**, **1g**) engaged in the reaction smoothly, leading to the products in 53% and 45% yields, respectively. The piperidine derivative (Table 1, **1i**) also showed comparable reactivity. Remarkably, the reaction of a bulky oxime (Table 1, **1h**) could also give a tertiary alkylation product **3h** in 30% yield. Interestingly, the hetero-cyclobutanone oximes oxetan-3-one oxime **1j** provided the corresponding coupling product **3j** in 62% yield. On the other hand, nonsymmetrical cyclobutanone oxime derivatives **1k**–**1o** delivered the olefination products **3k**–**3o** in 56–86% yields, in which C-C bond cleavage occurred selectively at the more hindered position. The yield can be up to 86% when **1n** was used as the substrate. In addition, bicyclo[3.2.0] substrate **1o** can generate the corresponding *trans*-product **3o** in 61% yield (Table 1, **3o**).

Encouraged by these results, we continued to explore the substrate generality with different olefins under the standard conditions. We first tested different 1,1-disubstituted alkenes. For example, *α*-methyl styrenes with electronic-withdrawing (F, Cl) or electronic-donating group (Me) at the *para*-position of the phenyl ring proceed smoothly to deliver the terminal and internal alkene mixtures with moderate to good yield (Table 1, **3p-3s**). Moreover, *α*-methyl 2-vinylnaphthalene **3t** also worked well in this condition and gave the terminal and internal mixture products in 62% yield. The reaction efficiency slightly dropped, only 35% or 36% yield could be obtained when we use simple styrene or 1-fluoro-4-vinylbenzene as the substrates, probably because of the high reactivity of the benzylic radical intermediate. To our delight, biologically important coumarin and high complicated diene could also give the product in 49% and 55% yields respectively (Table 1, **3w-3x**). Notably, the oxime derivatives of 2-heptanone, cyclopentanone and cyclohexanone were tested under our standard conditions as well, but no desired products could be detected.

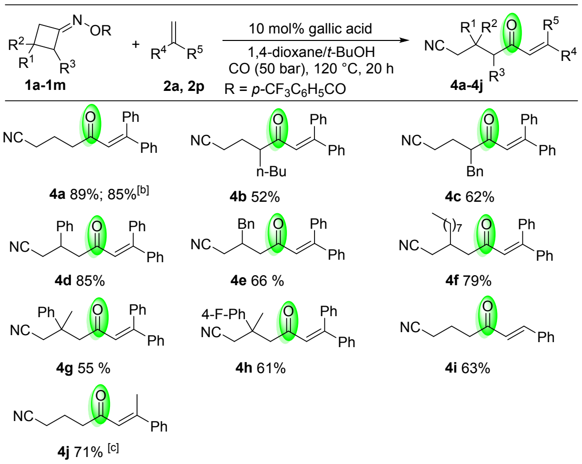
Table 1. Gallic acid-catalyzed alkenes synthesis.[a]



[a] Reaction conditions: **1a** (0.30 mmol, 1.0 equiv.), **2a** (0.45 mmol, 1.5 equiv.), gallic acid (10 mol%, 5.4 mg) in 1.5 mL tBuOH/1,4-dioxane (1:1) at 120 °C for 20 h, under argon, isolated yields. [b] **1a** (3.0 mmol, 1.0 equiv.), **2a** (4.5 mmol, 1.5 equiv.), gallic acid (10 mol%) in 10 mL tBuOH/1,4-dioxane (1:1), GC yield. [c] Trans isomer product. [d] 20 mol% gallic acid was used, the ratio of terminal and internal products were determined by GC.

Since our continual interests in carbonylation reactions and in order to further explore the potential application of this catalyst system. We investigated the radical carbonylation reactions[16] under the same conditions as well. To our delight, we get the desired carbonylation product in 89% yield by simply change the reaction concentration.[16a,17] With this positive result in hand, we then examined the scope of the alkyl-carbonylation reactions with a range of cyclobutaone oximes and olefins. As shown in Table 2, non-symmetrical cyclobutanone oxime derivatives work well in these carbonylation reactions, and give *α*,*β*-unsaturated ketones in 52% and 62% yields, respectively (Table 2, **4b** and **4c**). Regarding the mono-substitute symmetrical cyclobutaone oximes, we tested the phenyl, benzyl, and octanoyl groups. All of these substrates participated well in our standard conditions, and 3-phenylcyclobutan-1-one *O*-(4-(trifluoromethyl)benzoyl) oxime able to give the corresponding product with 85% yield (Table 2, **4d-4f**). In addition, di-substitute symmetrical cyclobutaone oximes proceeded smoothly to deliver *α*,*β*-unsaturated ketones in 55% and 61% yields (Table 2, **4g** and **4h**). Moreover, under the standard conditions, styrene and prop-1-en-2-ylbenzene also worked well, leading to the corresponding products in 63% and 71% yields, respectively (Table 2, **4i** and **4j**).

Table 2. Gallic acid-catalyzed ketones synthesis.[a]



[a] Reaction conditions: **1a** (0.15 mmol, 1.0 equiv.), **2a** (0.225 mmol, 1.5 equiv.), gallic acid (10 mol%, 2.7 mg) in 6 mL tBuOH/1,4-dioxane (1:1) at 120 °C for 20 h, under argon, isolated yields. [b] **1a** (3 mmol, 1.0 equiv.), **2a** (4.5 mmol, 1.5 equiv.), gallic acid (10 mol%) in 40 mL tBuOH/1,4-dioxane (1:1), GC yield. [c] The ratio of internal and terminal product = 3:1, the major product NMR was given.

In summary, a novel and versatile protocol for the (carbonylation-)alkylation reactions of cyclobutanone oximes with olefins promoted by bio-waste gallic acid has been developed. This green and sustainable reaction only need catalytic amount of gallic acid as the catalyst, no metal is required here. Therefore, it is an efficient and green approach for the synthesis of a wide range of diversely functionalized cyano-containing olefin and cyano-containing *α*,*β*-unsaturated ketone products that are difficult to access via other methods. Various cyclobutanone oximes and olefins can be transformed into the corresponding products in moderate to good yield. In addition, detailed EPR investigations and control experiment also showed clearly that this reaction go through a single-electron transfer mechanism. Further synthetic applications of gallic acid as catalyst are underway in our laboratory.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

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

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

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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