C–**C** Activation

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Copper-Catalyzed Intermolecular Heck-Like Coupling of Cyclobutanone Oximes Initiated by Selective C–C Bond Cleavage

Binlin Zhao and Zhuangzhi Shi*

Abstract: The first example of intermolecular olefination of cyclobutanone oximes with alkenes via selective C-C bond cleavage leading to the synthesis of nitriles in the presence of a cheap copper catalyst is reported. The procedure is distinguished by mild and safe reaction conditions that avoid ligand, oxidant, base, or toxic cyanide salt. A wide scope of cyclobutanones and olefin coupling components can be used without compromising efficiency and scalability. The alternative visible-light-driven photoredox process for this coupling reaction was also uncovered.

he activation and functionalization of C–C single bonds by transition-metal complexes is of fundamental interest and plays an important role in the synthesis of complex organic molecules.^[1] Because of the presence of multiple C-C bonds in an organic molecule with subtle difference in activation barrier, controlling the positional selectivity is the key challenge. Cyclobutanones and their derivatives are very useful intermediates that are widely used in total synthesis of nature products.^[2] Considerable attention has been turned to the selective functionalization via C-C bond cleavage over the years.^[3] Transition-metal catalysts, mainly rhodium,^[4] palladium,^[5] and nickel^[6] complexes, have been successfully used for the activation of C-C bonds in these compounds.^[7] Murakami and co-workers first reported an intramolecular cyclization of cyclobutanones bearing styrene-type olefin substituents to tricyclic ketone in good yields (Figure 1 a).^[8] In 2014, Dong and co-workers have developed a unique strategy to enable intramolecular cyclobutanone-olefin coupling through a Rh-catalysed cofactor-assisted C-C activation approach (Figure 1b).^[9] Herein, we have reported the first case on intermolecular Heck-like reaction of cyclobutanone derivatives with olefins in which nitrile products are derived by a formal Cu-catalyzed C-C cleavage of the cyclobutanone oximes avoiding the use of the toxic cyanide sources (Figure 1 c).

Although the Heck reaction has been widely studied, challenges in the field include the substrates that bear β -H, because their alkylmetal intermediate has the strong tendency to undergo a β -H elimination to generate conjugated olefin.^[10]

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Intramolecular addition of cyclobutanones with olefins:



Intermolecular olefination of cyclobutanone derivatives with olefins:

$$\begin{array}{c} N^{OBz} \\ R^1 \\ R^2 \\ R^3 \\ R^4 \end{array} + \begin{array}{c} R^8 \\ R^7 \end{array} + \begin{array}{c} R^8 \\ R^7 \end{array} \xrightarrow{cat [Cu]} \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \end{array} + \begin{array}{c} R^1 \\ R^2 \\ R^3 \\ R^4 \\ R^7 \\ R^$$

The challenges



Figure 1. Coupling of cyclobutanone derivatives with olefins via C–C bond cleavage.

For instance, in a seminal work by Nishimura and Uemura, a Pd-catalyzed intramolecular olefination of cyclobutanone oximes was described via β -carbon elimination, where the β -H elimination and migration of the formed double bond led to the conjugated α , β -unsaturated nitriles (Figure 1 d).^[11] Accordingly, to develop a general intermolecular cyclobutanone oxime–olefin coupling reaction that is broadly applicable for the synthesis of cyano-containing olefin products, the β -H elimination must be overcome and the scope of the cyclobutanones and olefins must be extended. Compared to the Pd catalyst, Cu salt^[12] is a promising redox catalyst for Heck-like reaction^[13] and free-radical addition of alkenes.^[14]

We began our investigations by monitoring the reactivity of cyclobutanone *O*-benzoyl oxime (**1a**) with 1,1-diphenylethylene (**2a**) in presence of copper catalysts (Table 1). While the reaction was found to be facile with 1.2 equiv of **2a** in the presence of the Cu(OTf)₂ catalyst (10 mol%) in a binary solvent system, 1,4-dioxane and trifluorotoluene ($\nu/\nu = 1:1$) at 100°C which afforded the 6,6-diphenylhex-5-enenitrile (**3aa**) in 90% isolated yield (entry 1). The copper salt is crucial for the success (entry 2). Either 1,4-dioxane or trifluorotoluene as sole solvent provided lower yield (entries 3,4). Intriguingly, changing the ratio of two components **1a** and **2a** to 2:1 did not influence the yield at all, which greatly improved the practicality (entry 5). At a lower temperature, 70°C the

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Table 1: Reaction development.^[a]



[a] Standard conditions: **1a** (0.20 mmol, 1.0 equiv), **2a** (0.24 mmol, 1.2 equiv) in 2 mL PhCF₃ and 1,4-dioxane (1:1) at 100 °C for 12 h, under argon. [b] Determined by GC. [c] Isolated yields. [d] **1a**' = cyclobutanone *O*-(4-nitrobenzoyl) oxime. [e] **1a**'' = Cyclobutanone *O*-perfluorobenzoyl oxime.

results were found inferior than that observed under the optimal conditions (entry 6). Interestingly, other copper catalysts such as CuI and even copper powder were also effective for this transformation albeit with lower yields (entries 7,8). Further exploration showed that the cyclobutanone *O*-(4-nitrobenzoyl) oxime (**1**a') and *O*-perfluorobenzoyl oxime (**1**a'') could also be converted into **3 aa** in very excellent yield (entries 9,10). Synthesis of **3 aa** could not be observed under palladium catalysis (entry 11).^[11] However, the use of an iridium complex [Ir(cod)Cl]₂^[15] instead of Cu(OTf)₂ could result formation of the desired product **3 aa** in 35% yield (entry 12).

With the set of optimized reaction conditions in hand, we first examined the scope of various olefin motifs in this C-C cleavage event (Table 2). Using this new method, the reaction of 1a and 2a could be efficiently accessed on gram scale without compromising its efficiency. Olefins 2b-2c delivered the products 3ab and 3ac in moderate yields along with a small amount of isomer formation. It is worth noting that styrenes 2d-2g bearing methyl, Br, BPin, and 2-vinylnaphthalene (2h) only yielded *trans*-products. Importantly, diene 2i and envne 2j reacted smoothly with 1a to produce the nitriles 3ah-3aj in 58-64% yields. N-Acetyl-1-phenylethenamine (2k) delivered a mixture of Z/E isomers (Z/E = 83:17) in 47% yield. Net benzofuran coupling adduct 3al was obtained in 84% yield by reaction of 1a with 3-methylene-2,3-dihydrobenzofuran (21). Alkylcyanation of vinylestrone 2m could produce 3am in 65% yield. Late-stage modification^[16] of exemestane proceeded with 1a to form a double bond migration endo-product 3an with the normal exoproducts in a 64:36 ratio. Trenbolone acetate (10) is an extremely powerful anabolic steroid with three different double bonds, reacted smoothly to generate 3ao in 58% yield with sole regioselectivity. Coumarin and its derivatives 1p-1t with remarkable biological activities, such as antitumor, anti-

Table 2: Scope of the olefins.^[a]



[a] Reaction conditions: 10 mol% Cu(OTf)₂, **1a** (0.20 mmol, 1.0 equiv), **2** (0.24 mmol, 1.2 equiv) in 2 mL PhCF₃ and 1,4-dioxane (1:1) at 100°C for 12 h, under argon, isolated yields. [b] 10 mol% Cu(OTf)₂, **1a** (1.1 g, 6.0 mmol), **2a** (1.3 g, 7.2 mmol) in 60 mL PhCF₃ and 1,4-dioxane (1:1) at 100°C for 12 h, under argon, isolated yield. [c] Determined by GC-MS and/or ¹H NMR. [d] Using **1a** (2.0 equiv). [e] At 60°C. [f] Using **1a** (4.0 equiv).

HIV, antioxidant, antibacterial, antiinflammatory, and antipsychotic activity,^[17] were exposed to the reaction condition affording the structural modified products **3ap–3at** with sole site-selectivity as well.

To further explore the potential of this novel C-C olefination reaction, a series of cyclobutanone derivatives were examined (Table 3). Symmetrical cyclobutanone derivatives with a wide array of functional groups including phenyl (1b), benzyl (1c), ester (1d), cyano (1e), ether (1f), and 4-methoxy-2-methyl-4-oxobutan-2-yl (1g) could be transferred to the products **3ba-3ga** in 43–89% yields. Di-substituted cyclobutanone derivatives **1h-1i** underwent facile olefina-

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Table 3: Scope of the cyclobutanone oximes.^[a]



[a] Reaction conditions: 10 mol% Cu(OTf)₂, **1** (0.20 mmol, 1.0 equiv), **2** (0.24 mmol, 1.2 equiv) in 2 mL PhCF₃ and 1,4-dioxane (1:1) at 100 °C for 12 h, under argon, isolated yields. [b] At 80 °C. [c] Determined by GC-MS and/or ¹H NMR. [d] At 40 °C.

tion. The piperidine derivative 1j also showed comparable reactivity. Remarkably, the reaction of a bulky oxime 1k could provide a tertiary alkylation product 3ka in 58% yield. Nonsymmetrical cyclobutanone derivatives 11-10 delivered the olefination products **3la-3oa** in 68-91% yields, in which C-C bond cleavage occurred selectively at the more hindered position. Z/E isomers of bicyclo[4.2.0] type oxime **1p** were separable by column chromatography, which exhibited slight difference in reactivity and generated *trans*-product 3ga as a major product. Moreover, the conversion of bicyclo[3.2.0] substrate 1q had same stereochemistry with excellent diasteroemeric ratio (93:7). Interestingly, oxetan-3-one oxime 1r provided the corresponding nitrile 3ra in 55% yield. In addition, benzocyclobutenone derivatives 1s-1u also worked well under the standard reaction conditions forming the benzonitrile products 3sa-3ua in 68-93% yields with sole regioselectivity. Unfortunately, example of less-strained substrates such as 1v only provided the desired product 3va in trace amount under the current reaction conditions.

Several experiments were conducted to get insight into the potential mechanism of this transformation. The reaction with TEMPO, largely inhibited the reaction to form the product **3aa**. Formation of alkylated TEMPO **4** also suggested the existence of radical species in the reaction (Scheme 1 a). Moreover, submitting the olefin **5** to the standard conditions afforded dihydronaphthalene **7** in 35% yield. The formation of **7** can be accounted by invoking the benzylic radical **6** that underwent fragmentation and cyclization (Scheme 1 b). When the reaction mixture was irradiated with visible light in the presence of fac-[Ir(ppy)₃], a common visible light-mediated photoredox catalysis, the substrates **1a** and **1a'** were in poor conversion. However, we isolated the desired product **3aa** in 73% yield when employing *O*-perfluorobenzoyl oxime **1a''**.^[18] Further analysis of oximes **1a–1a''** by cyclic voltammetry revealed irreversible reduction profiles that are in accordance with our experimental results (see the Supporting Information). According to the electro-



Scheme 1. Mechanistic experiments.

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chemical scale, the $E_{1/2}$ reduction potential of oxime **1a** was completely unsuitable for SET in the excited state of the *Ir^{III}. This photoredox process not only provided an alternative approach for this coupling reaction, but also further demonstrated the high reactivity of copper catalysis in this radical chemistry (Scheme 1 c).

On the basis of the above experimental results, a mechanism has been proposed as shown in Figure 2. The reaction starts with the generation of cyclobutylideneiminyl radical



Figure 2. Proposed catalytic cycle.

species $A^{[19]}$ from compound 1 in the presence of Cu^{*n*} catalyst affording a high reactive alkyl radical B via homolytic C–C bond cleavage. Then, addition of B to 2 generates a more stabilized, less reactive, and more easily oxidizable radical C. This intermediate can be further oxidized by Cu^{*n*+1} species to produce an intermediate D with concomitant formation of a Cu^{*n*} species. Finally, the cationic intermediate D undergoes elimination reaction to provide the Heck-like product 3. Because copper salts from 0 to +2 valent, all can participate in this reaction, the exact valent of copper catalyst is currently unclear.

In conclusion, we reported the first copper-catalyzed intermolecular olefination of cyclobutanone oximes initiated by selective C–C bond cleavage. The reaction is applicable to a wide range of olefins and cyclobutanone derivatives to provide cyano-containing olefin products that are otherwise difficult to access. Studies to determine further mechanistic details of this process and to expand the scope of synthetic application are underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: copper \cdot cyclobutanone \cdot olefination \cdot oximes \cdot radicals

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Copper-Catalyzed Intermolecular Heck-Like Coupling of Cyclobutanone Oximes Initiated by Selective C-C Bond Cleavage



No construction without destruction: A copper-catalyzed intermolecular olefination of cyclobutanone oximes with alkenes by C–C activation has been established. The method features mild and safe reaction conditions that avoid

ligand, oxidant, base, or toxic cyanide salt, and a wide scope of cyclobutanones and olefin coupling components can be used without compromising efficiency and scalability.

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