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Direct C–H Cyanoalkylation of Heteroaromatic *N*-Oxides and Quinones via C–C Bond Cleavage of Cyclobutanone Oximes

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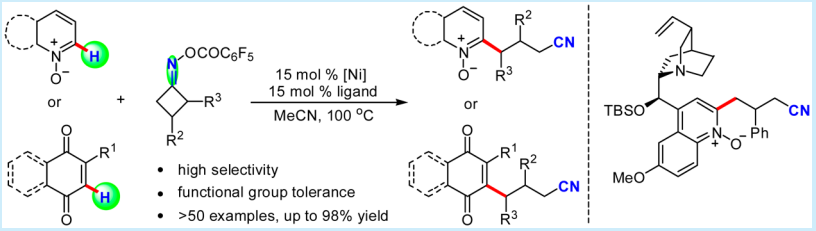
Supporting Information



ABSTRACT: A direct C–H cyanoalkylation of heteroaromatic *N*-oxides and quinones with cyclobutanone oximes is reported. This redox-neutral, operationally simple cyanoalkylation reaction is successfully amenable to a wide range of heteroaromatic *N*-oxides, quinones, and cyclobutanone oximes. A novel catalytic system consisting of a nickel source proved crucial for cleavage of the C–C bond of cyclobutanone oximes and for selective C–C bond formation over β-hydride elimination. Mechanistic studies suggest that a radical intermediate might be involved in this transformation.

Alkylnitriles represent a privileged class of structural motifs that can be found in many natural products and pharmaceutical compounds.[1] Furthermore, cyanoalkyl moieties are one of the most versatile building blocks in organic synthesis owing to their easy conversions to other functional groups, such as amines, amides, carboxylic acids, and heterocycles.[2] As a result, diverse methods for the synthesis of alkylnitriles have been developed over the past few decades.[3] One traditional method for alkylnitrile synthesis is based on the addition of hydrogen cyanide (HCN) or the related less volatile precursor, acetone cyanohydrin (TMSCN), to alkenes.[4a] The use of toxic HCN is associated with a somewhat troublesome gas handling procedure, which to some extent limits their further applications. In addition, some different approaches to structurally diverse alkylnitriles, including cyanation of alkyl halides,[4b] dehydration of amides or aldoximes,[4c–e] dehydrogenation of amines,[4f,g] direct activation of nonactivated alkylnitriles[2a,4h,l] and others,[5] have also been developed. More recently, remarkable advances have been made in the efficient and practical synthesis of alkylnitriles.[5e,f] Despite this significant progress, new methods for incorporation of cyanoalkyl groups, especially those bearing longer aliphatic chains into organic skeletons, are still quite challenging and rare.[3]

Transition-metal-catalyzed carbon–carbon bond cleavage of strained rings has emerged as a useful and powerful tool for carbon–carbon and carbon–heteroatom bond formations.[6] In this field, strained cyclobutanone oximes and their derivatives are efficient substrates to obtain alkylnitriles through the β-carbon elimination pathway. In 1991, Zard and co-worker reported a radical C–C bond cleavage of cyclobutanone sulfenylimines or carboxymethyl oximes to alkylnitriles, wherein an iminyl radical intermediate was involved (Figure 1, route a).[7] Subsequently,

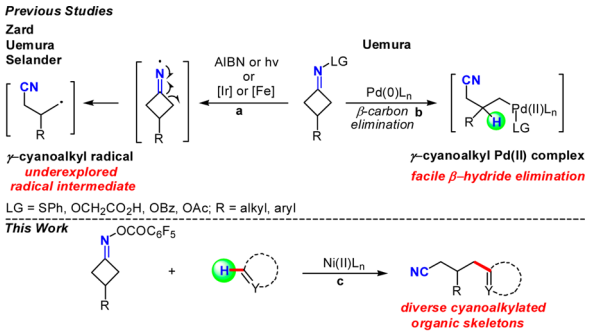


Figure 1. Carbon–carbon bond cleavage of cyclobutanone oximes.

Uemura and co-workers disclosed another alternative to nitriles through the palladium-catalyzed ring opening of cyclobutanone oximes. In this reaction, the cyanoalkylpalladium species was formed first via β-carbon elimination, which underwent β-hydride elimination to provide the alkenylnitriles (route b).[8] Although active intermediates, such as γ-cyanoalkyl radical and γ-cyanoalkyl metal complex, were formed in those processes, further studies on their diverse transformations were less exploited. Due to our continuous interest in C–C bond cleavage reactions,[9] we expect to develop novel catalytic systems, wherein the β-hydrogen elimination of cyanoalkyl metal intermediate could be inhibited, so that further transformations can be performed.[7] Herein, we report the first nickel-catalyzed direct C–H cyanoalkylation of electron-deficient heteroaromatic *N*-

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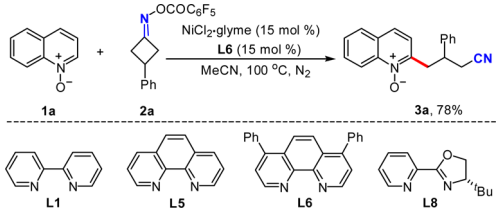
oxides and quinones with cyclobutanone oximes under redox-neutral conditions (route c).

We started our investigation by treatment of quinoline *N*-oxide **1a** and cyclobutanone pentafluorobenzoyloxime **2a** with nickel catalysts, which exhibited high reactivity toward alkyl partners and favorable single-electron redox potentials.[10] Satisfactorily, the reaction was proven uniquely effective in the presence of 10 mol % of $NiCl_2$·glyme and bipyridine in CH_3CN at 100 °C, leading to the desired product **3a** in 46% yield (Table 1, entry 1; for details, see Supporting Information (SI)).

Table 1. Reaction Optimization[a]



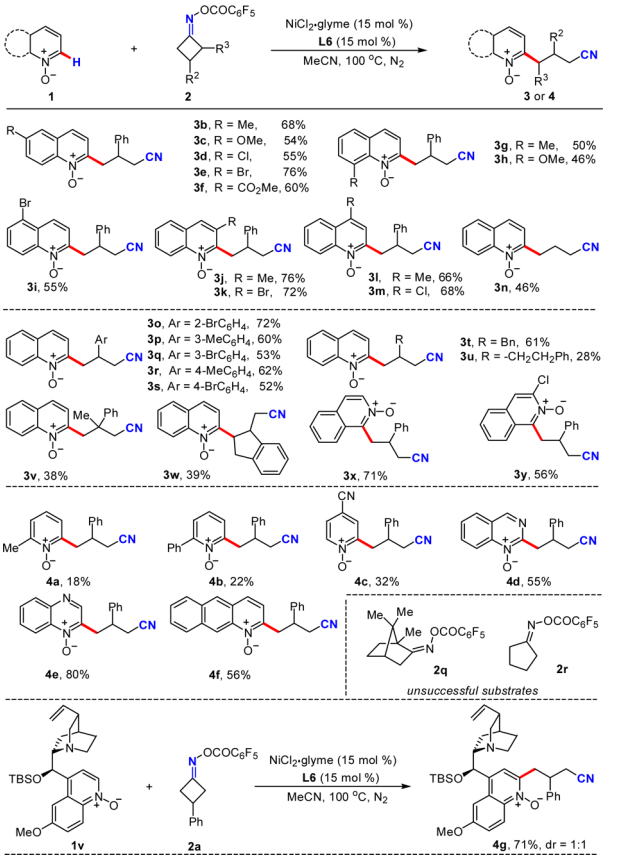
entry	deviation from above	yield (%)[b]
1	10 mol % of **L1** as ligand	46
2	10 mol % of **L5** as ligand	66
3	10 mol % of **L6** as ligand	71
4	10 mol % of **L8** as ligand	62
5	10 mol % of $FeCl_2$ as catalyst	51
6	10 mol % of $CoCl_2$ as catalyst	60
7	10 mol % of $[Ir(cod)Cl]_2$ as catalyst	11
8	without catalyst	nr[c]

[a]Reaction conditions: 10 or 15 mol % of catalyst and ligand, **1a** (0.3 mmol 1.5 equiv), **2a** (0.2 mmol, 1.0 equiv), CH_3CN (2 mL), 100 °C, 16 h. [b]Yield of isolated product. [c]No reaction.

Meanwhile, phenanthrolines **L5** and **L6** and oxazolin **L8** were also examined as ligand, and bathophenanthroline **L6** gave the best result (entries 2−4). Subsequently, a screening of catalysts was performed carefully (entries 5−7). The iron and copper catalysts also exhibited similar catalytic activity, but $[Ir(cod)Cl]_2$ only led to the desired product **3a** in 11% yield.[7c] Further investigation revealed that 15 mol % of catalyst and ligand loading improved the yield to 78%, whereas the 7.5 and 20 mol % loading gave somewhat lower yields. Control experiments disclosed that no desired product was detected in the absence of catalyst (entry 8). It is noteworthy to mention that the alkenylnitrile byproduct generated through *β*-hydride elimination was not observed in all those cases, which might be due to the use of nickel catalyst as well as the radical pathway.[10]

With optimized conditions in hand, we sought to examine the scope and generality of this reaction. As shown in Scheme 1, a variety of quinoline *N*-oxides bearing electron-donating or electron-withdrawing groups at the 6-position of the aromatic ring reacted smoothly with **2a** to give the corresponding products **3b−f** in moderate to good yields. 8-Methyl- and 8-methoxy-substituted quinoline *N*-oxides were also good substrates, furnishing the desired products **3g** and **3h** in 50 and 46% yields, respectively. Notably, 3-, 5-, or 6-bromo-substituted quinoline *N*-oxides **1e**, **1i**, and **1k** also survived this transformation and gave the desired products in good yields (**3e**, **3i**, and **3k**), thereby offering opportunities for further functionalization on the product. To our delight, the reaction of sterically hindered 3-methyl- or 3-bromoquinoline *N*-oxides also proceeded well under the optimized conditions, leading to the corresponding 2-cyanoalkyled products **3j** or **3k** in 76 or 72% yields, respectively.

Scheme 1. Scope of Direct C−H Cyanoalkylation of Heteroaromatic *N*-Oxides with Cyclobutanone Oximes



Additionally, 4-methyl- and 4-chloroquinoline *N*-oxides were also suitable substrates (**3l** and **3m**). Subsequently, the scope of cyclobutanone oximes was investigated. The simple substrate derived from cyclobutanone also participated well in this coupling process (**3n**). A wide range of cyclobutanone oximes containing aryl, benzyl, or alkyl groups on the 3-position were also efficiently converted to the corresponding products **3o−u** in moderate to good yields. The 3,3-disubstituted and tricyclic cyclobutanone oximes were also applicable to the reaction, albeit in somewhat low yields (**3v** and **3w**). Notably, the C−C bond cleavage of tricyclic cyclobutanone oximes occurred at the sterically more hindered site regioselectively, which can be attributed to the stability of the intermediate radical.[7c] Unfortunately, the less-strained substrates such as camphor oxime **2q** and cyclopentanone oxime **2r** failed to provide any desired product. Besides quinoline *N*-oxides, other heteroaromatic *N*-oxides, including isoquinoline, pyridine, quinazoline, quinoxaline, and benzoquinoline *N*-oxides, were also compatible with the reaction conditions, providing the corresponding products in acceptable yields (**3x**, **3y**, **4a−f**). Remarkably, pharmaceuticals such as cinchonine *N*-oxide could also give the desired cyanoalkylated product **4g** in 71% yield.

Encouraged by the above results, we turned our efforts toward extending this direct C−H cyanoalkylation protocol to other attractive targets. Quinones were considered to be quite important structural motifs in many biologically active natural products, pharmaceuticals, and functional materials. Recently, great efforts have been devoted to direct C−H functionalization of quinones, but it is still deficient due to relatively few coupling partners and requirement of excessive oxidants and noble

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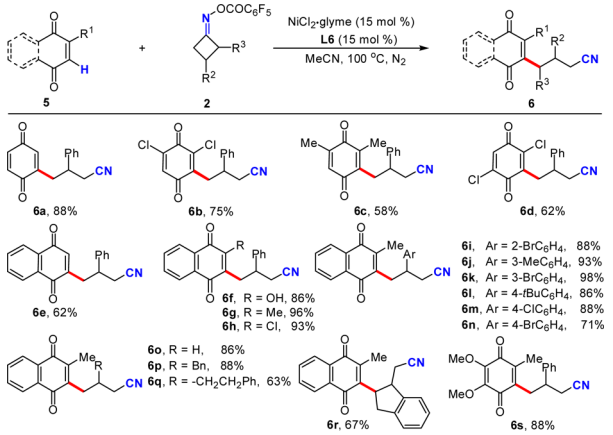
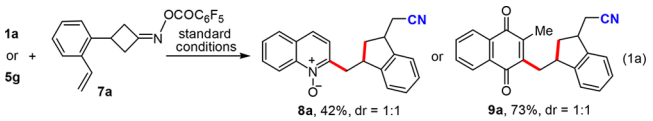
metals.[11] Therefore, we aim to develop an efficient and practical synthesis of cyanoalkylated quinone derivatives. To our delight, the reaction of benzoquinone with cyclobutanone oxime **2a** proceeded very well under the above reaction conditions, affording the desired product **6a** in 88% yields (Scheme 2).

Scheme 2. Scope of Direct C−H Cyanoalkylation of Quinones with Cyclobutanone Oximes



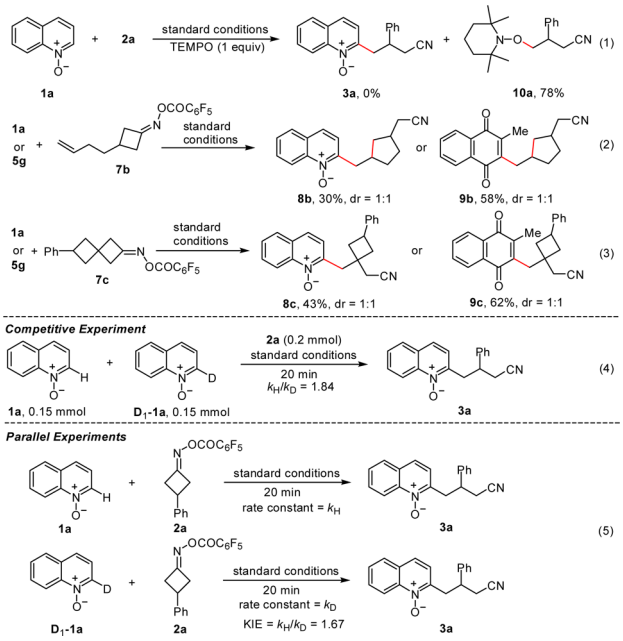
Dichloro- or dimethyl-substituted benzoquinones were successfully converted into the corresponding products **6b−d** in moderate yields. Naphthoquinone was also found to be a suitable substrate for this reaction and gave the desired product **6e** in 62% yield. Notably, an unprotected hydroxyl group was well tolerated in this reaction, providing good opportunities for further modifications (**6f**). The 2-methyl- or 2-chloronaphthoquinone also resulted in the desired products **6g** and **6h** in excellent yields. More importantly, a variety of substituted cyclobutanone oximes bearing aryl, benzyl, or alkyl substituents underwent direct C−H cyanoalkylation efficiently to afford the cyanoalkylated naphthoquinones **6i−q** in good to excellent yields. When tricyclic cyclobutanone oxime was subjected to the reaction, the cyanoalkylated product **6r** was isolated in 67% yield. Significantly, the apoptosis inducer coenzyme Q_0 also furnished the target product **6s** in 88% yield.

Interestingly, cyclobutanone oxime **7a** containing an *o*-substituted styryl group at the 3-position also worked well with **1a** or **5g** under the nickel catalytic system, affording the anticipated product **8a** or **9a** in moderate yields, respectively. In this transformation, a tandem ring-opening/cyclization/coupling process is involved (eq 1a).



To probe the mechanism of this reaction, some control experiments were conducted (for details, see SI). When TEMPO, a typical radical scavenger, was added to the standard system, the reaction was suppressed completely, and only cyanoalkyl-TEMPO adduct **10a** was isolated in 78% yield (Scheme 3, eq 1). As expected, the butylated hydroxytoluene also inhibited the reaction remarkably. These results suggest that a free radical process would be involved. Subsequently, some radical clock experiments were performed with substituted cyclobutanone oximes **7b** and **7c**. The reaction of quinoline *N*-oxide **1a** or 2-methylnaphthoquinone **5g** with **7b** under standard

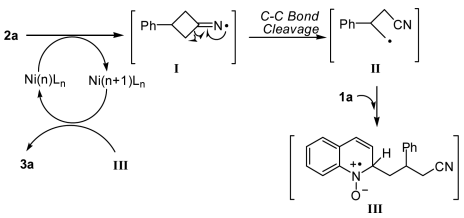
Scheme 3. Mechanistic Studies



conditions gave the corresponding annulated products **8b** or **9b** in 30 or 58% yields, respectively, as sole product (eq 2). Unexpectedly, treatment **1a** and **5g** with **7c** resulted in the products **8c** and **9c** in moderate yields, respectively (eq 3). Furthermore, the intermolecular competitive and parallel experiments using **1a** and deuterated **1a** with **2a** were also conducted. The kinetic isotope effect values of 1.84 and 1.67 were observed (eqs 4 and 5). On the other hand, heat-induced activation of cyclobutanone oximes to generate iminyl radicals was ruled out by a contrast experiment.[12]

Based upon the preliminary results, a possible mechanism is proposed (Scheme 4). First, single-electron transfer from the Ni

Scheme 4. Proposed Mechanism



complex to cyclobutanone oxime **2a** leads to the iminyl radical **I**, which gives the radical **II** via a *β*-carbon elimination process. Second, addition of radical **II** to quinoline *N*-oxide **1a** affords radical cation **III**, which undergoes single-electron oxidation by Ni catalyst followed by the loss of H^+ to produce the product **3a**. More studies are underway to elucidate the detailed mechanism of this transformation.

To test the practicability of this protocol, the reaction was performed on a gram scale (3 mmol). Satisfyingly, the desired product **3a** was obtained in 70% yield (for details, see SI). To further demonstrate the synthetic utility of this reaction, derivatization reactions of the cyanoalkylated quinoline *N*-oxide **3a** were carried out. **3a** could be easily reduced by treatment with $PhB(OH)_2$ to furnish the corresponding quinoline **11a** in 90% yield. The CN group of the **11a** could be efficiently transformed into carboxylic acid **12a** through basic

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hydrolysis. Moreover, **11a** could also be converted to amide **13a** by H_2O_2 oxidation in moderate yield. Reduction of **11a** with $LiAlH_4$ gave the amine **14a** in 66% yield. Finally, upon treatment with acetic anhydride, **3a** was easily converted to **15a** in 73% yield.[13]

In summary, we have developed a nickel-catalyzed direct C−H cyanoalkylation of heteroaromatic *N*-oxides and quinones with cyclobutanone oximes. This novel nickel catalytic system was first applied to the ring-opening reaction of cyclobutanone oximes, which allows for direct installation of structurally diverse cyanoalkyl groups into the electron-deficient molecules. This protocol exhibits good compatibility with a broad range of heteroaromatic *N*-oxides, quinones, as well as cyclobutanone oximes. This work represents one of the examples of C−C bond formation via catalytic C−C cleavage of cyclobutanone oximes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02902.

Experimental procedures and spectroscopic data of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Professor Herbert Mayr on the occasion of his 70th birthday.

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