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Radical-Induced Ring-Opening and Reconstruction of Cyclobutanone Oxime Esters

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The first example of intramolecular ring-opening and reconstruction of cyclobutanone oxime esters via selective C-C bond cleavage leading to the synthesis of 3, 4-dihydronaphthalene-2-carbonitriles in the presence of a cheap copper catalyst has been reported. The protocol is distinguished by mild and safe reaction conditions that avoid ligand, oxidant, base, toxic cyanide salt and exhibited wide scope of cyclobutanones without compromising its efficiency and scalability. The alternative visible-light-driven photoredox process for this coupling reaction was also uncovered.

The dissociation and recombination of C-C bond cleavage is of fundamental interest and plays an important role in the synthesis of complex organic molecules.[1] Due to the presence of multiple C–C bonds in an organic compound with subtle difference in activation barrier, controlling the site-selectivity represents a key challenge. Cyclobutanones are a privileged simple scaffold widely applied in the synthesis of pharmaceuticals, natural products and bioactive molecules.[2] Considerable attention has been turned to the selective functionalization of cyclobutanones and the derivatives[3] *via* C–C bond cleavage over the years. Since the pioneering work of Zard[4] and Uemura,[5] an array of C–C bond β-scission reactions in cyclobutanone oximes and other derivatives via iminyl radicals[6] have been extensively exploited to construct carbon-carbon and carbon-heteroatom bonds by transition-metal catalysis[7] and visible-light photocatalysis.[8]

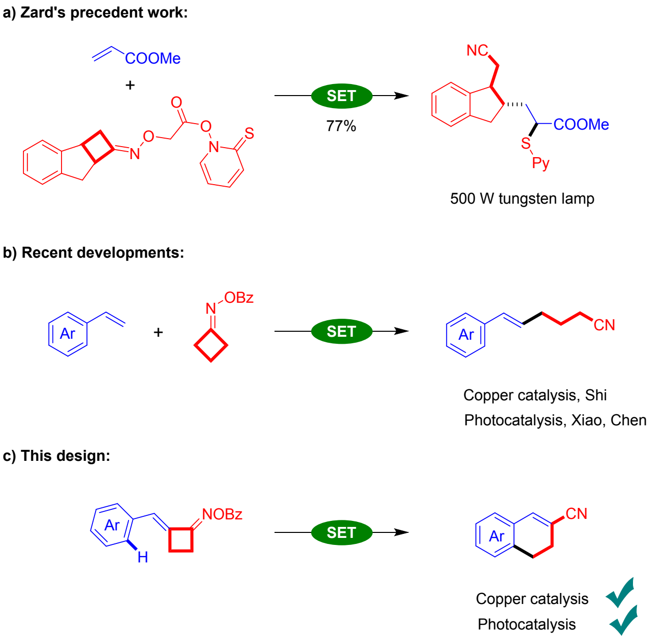

Figure 1 Radical Induced Ring-Opening and Reconstruction of Cyclobutanone Oximes.

As early in 1994, Zard group reported a sequential ring opening/addition of cyclobutanone oximes and methyl acrylate using stiochiometric radical initiators or UV irradiation (Figure 1a).[4c] In 2017, we[9] and Xiao[10] group independently extended this elegant chemistry to intermolecular olefination of cyclobutanone oxime esters[11] with alkenes, triggered by copper catalysis, or photocatalysis under visible-light (Figure 1b). Herein, we report the rational design of a series of 2-benzylidenecyclobutan-1-one derivatives for ring-opening and reconstruction via C–C bond cleavage to synthesize various 3, 4-dihydronaphthalene derivatives (Figure 1c). Notably, Dong and coworkers recently uncovered a general approach to the catalytic activation of C–C bonds in simple cyclopentanones and some cyclohexanones undergoing ring-opening and reconstruction by combination of a rhodium pre-catalyst, an N-heterocyclic carbene ligand and an amino-pyridine co-catalyst, in which the in situ formed cycloketimine act as a key intermediate.[12] This radical-induced strategy is based on a novel fragmentation-rearrangement sequence of cyclobutanone oxime esters using copper catalysis or photocatalysis.

Under the inspiration of our copper chemistry, we first prepared 2-((E)-benzylidene)cyclobutan-1-one O-benzoyl oxime (**1a**) as a model substrate and copper salts was chosen as the radical activator to investigate the possibility of the ring-opening and reconstruction reactions as shown in Table 1. To our delight, we

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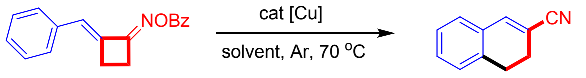
Table 1 Optimization studies[a]



1a **2a**

entry	catalyst	solvent	T (°C)	time (h)	Yield (%)[b]
1	$Cu(OTf)_2$	1,4-dioxane	70	12	53
2	$Cu(OTf)_2$	DMF	70	12	54
3	$Cu(OTf)_2$	THF	70	12	78
4	$Cu(OTf)_2$	ether	70	12	trace
5	$Cu(acac)_2$	THF	70	12	32
6	$CuSO_4$	THF	70	12	45
7	CuF_2	THF	70	12	51
8	$Cu(OTf)_2$	THF	50	12	38
9	$Cu(OTf)_2$	THF	90	12	45
10	**$Cu(OTf)_2$**	**THF**	**70**	**3**	**88 (85)**[c]
11	$Cu(OTf)_2$	THF	70	24	68
12	-	THF	70	3	0

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[a] **1a** (0.2mmol), 5 mol% of catalyst in solvent (0.1 M) under Ar at 70 °C. [b] GC-MS yield using dodecane as internal standard. [c] isolated yield.

obtained the product 3,4-dihydronaphthalene-2-carbonitrile (**2a**) in 53% yield, when the reaction was performed in the presence of $Cu(OTf)_2$ (5.0 mol %) in 1,4- dioxane at 70 °C for 12 hours (entry 1). A brief evaluation of solvents showed that THF was superior to other investigated solvents (entry 2), and the yield of desired product **2a** was improved to 78% (entry 3). Other copper salts such as $Cu(acac)_2$, $CuSO_4$ or CuF_2 led to lower yield of **2a** compared with the performance of $Cu(OTf)_2$ (entries 5-7). Under these reaction conditions, changing the temperature failed to enhance the efficiency of the transformation (entries 8-9). Critical to the promotion of this reaction was to shorten the reaction time to 3 hours, in which 85% yield of **2a** was obtained (entry 10). The decrease in yield with an increase in time is likely due to the decomposition of product **2a** under the reaction conditions (entry 11). Finally, control experiment confirmed the coupling process did not occur in the absence of the copper catalyst (entry 12).

With the optimized reaction conditions in hand, the scope of this copper-catalyzed C-C bond cleavage was then examined (Table 2). In general, a wide range of cyclobutanone derivatives containing electronically varied groups reacted smoothly, yielding the corresponding products, in modest to excellent yields. Substrates with different aryl moieties bearing electron-neutral, donating and withdrawing substituents including methyl (**1b-c**), ether (**1d-e**), mercapto (**1f**), F (**1g**), Cl (**1h**), Br (**1i**), and CF_3 (**1j**) groups at the ortho, and para position underwent facile ring-opening and reconstruction. It is note to worth that some hetero aromatic rings including furan (**1k**) and thiophene (**1l**) were also compatible well with the mild conditions and the corresponding products were obtained in good yields with excellent regioselectivity (**2k-2l**). In case of a β-naphthalene substituted substrate **1m**, we could furnish the cyclization product **2m** in high yields with good regioselectivity. Next we tested other substrates with varieties on the cyclobutanone rings. The cyclobutanone oximes with a phenyl, benzyl and dimethyl groups on the cyclobutanone rings were

Table 2 Substrate Scope[a]

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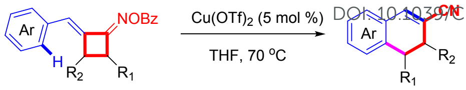
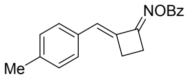
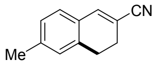
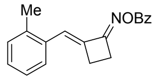
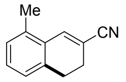
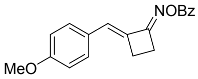
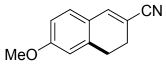
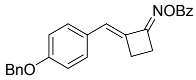
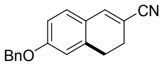
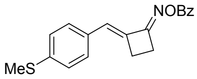
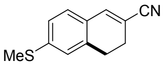
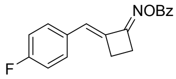
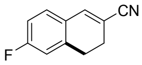
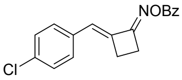
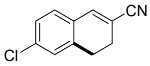
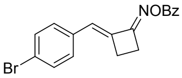
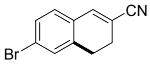
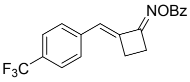
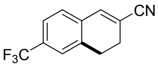
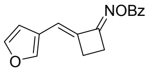
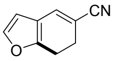
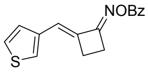
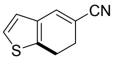
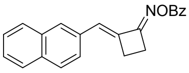
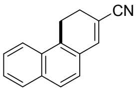
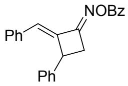
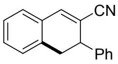
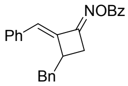
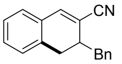
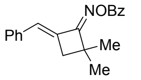
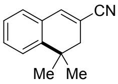


1 **2**

Entry	Subatrates **1**		Products **2**		Yield
1		**1b**		**2b**	82%
2		**1c**		**2c**	81%
3		**1d**		**2d**	65%
4		**1e**		**2e**	92%
5		**1f**		**2f**	53%
6		**1g**		**2g**	83%
7		**1h**		**2h**	89%
8		**1i**		**2i**	81%
9		**1j**		**2j**	66%
10		**1k**		**2k**	72%
11		**1l**		**2l**	78%
12		**1m**		**2m**	66% (93:7)
13		**1n**		**2n**	35%[b]
14		**1o**		**2o**	55%[b]
15		**1p**		**2p**	67%[b]

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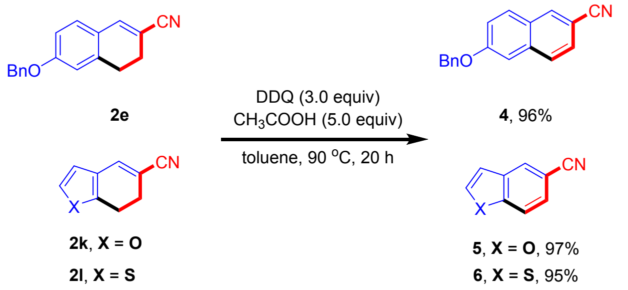
[a] Unless otherwise noted the reactions were carried out on a 0.2 mmol scale of **1** in the presence of $Cu(OTf)_2$ (5 mol%) in THF (2 mL) at 70 °C under Ar atmosphere for 3 hours . Yields of the isolated yields. [b] For 12 hours.

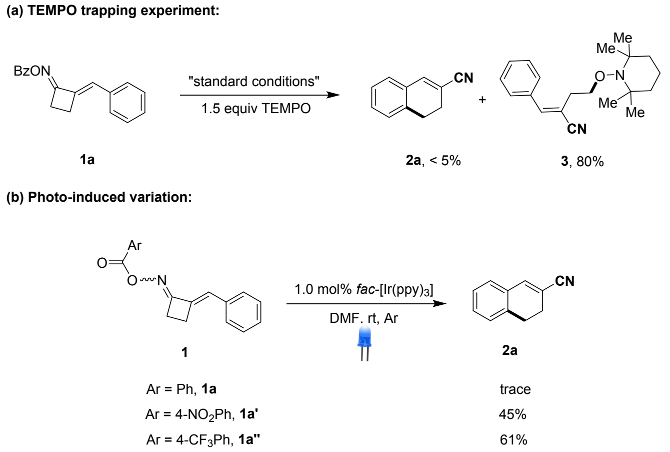
prepared and applied under the standard conditions delivering the 3,4-dihydronaphthalene-2-carbonitrile derivatives in 35% to 67% yields (**2n**-**2p**).

Arylnitriles are ubiquitous in bioactive natural products, pharmaceutically relevant molecules and electronic materials.[13] Furthermore, the nitrile group plays an important role in the area of synthesis chemistry owing to its robust transformable properties.[14] Having established this strategy for generating the 3,4-dihydronaphthalene-2-carbonitrile frameworks, which are valuable precursors for the construction of arylnitriles. This is documented in Scheme 4 by the highly selective DDQ oxidation of **2e** , **2k** and **2l** to give the corresponding arylnitriles **4**, **5** and **6** in excellent yields respectively.



Scheme 1. Synthetic Applications and Transformations

To get insight into the possible mechanism of copper-catalyzed intramolecular radical cyclization. TEMPO radical quenching experiment was carried out with the oxime **1a**. The radical cyclization product **2a** was inhibited and considerable amount of distal carbon-TEMPO adduct **3** was formed (Scheme 2a). This result suggested that the reaction occurred via a radical-mediated pathway, and the distal carbon radical was the important intermediate in this transformation. We also tried the photocatalytic reactions to find an alternative reaction system to realize the intramolecular C-C bond cleavage/C-C bond formation. We tested three oximes with different redox potentials under blue LEDs (5 W) irradiation with *fac*-[Ir(ppy)$_3$] as the photocatalyst giving different yields of the desired products respectively (Scheme 2b). The performance of the conversion was closely associated with the different redox potentials of the substrates and the 4-CF$_3$Ph substituted oxime was chosen as a good candidate exhibiting well compatibility with the photo-induced reaction system.



Scheme 2. Mechanistic Experiments

Based on the experimental results described above and the previous literatures, we proposed a possible mechanism depicted in Scheme 3. The iminyl radical **A** was generated by the copper salt via the single electron transfer (SET) reduction process with a release of anion **B** and Cu^{n+1} species. Subsequently, radical **A** was transformed to a distal radical **C** driven by the ring strain via a β-scission of C-C bond. Then an intramolecular radical cyclization happened between the carbon radical and the aromatic ring providing a reduction potential intermediate **D**. Finally, **D** was oxidized to a cyclization cation **E** by Cu^{n+1} to form the desired product, and the regenerated Cu^{n} was put into the next catalytic cycle.

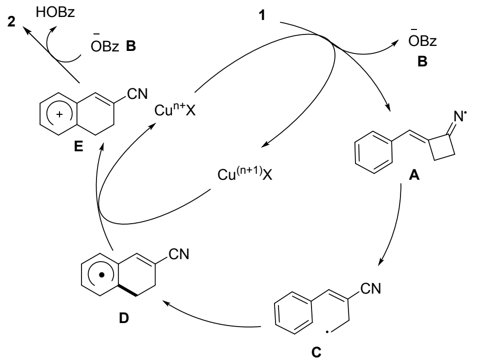


Figure 2 Proposed catalytic cycle

In conclusion, we reported the first carbon-radical cyclization enabled by copper-catalyzed selective C-C bond cleavage of cyclobutanone oximes. This method was applied for the synthesis of 3,4-dihydronaphthalene-2-carbonitriles containing diverse fuctional groups. Moreover, these products could be efficiently converted into varieties of arylnitriles. The primary mechanistic experiments suggested that a radical-mediated sequence was involved in this transformation. A photo-induced strategy was also developed for an alternative approach for this ring-opening and reconstruction.

We thank the "1000-Youth Talents Plan", the "Jiangsu Specially-Appointed Professor Plan", NSF of China (Grant 2167020084), Jiangsu Provincial Nature Science Foundation (SBK2016021885), the Top-notch Academic Programs Project of Jiangsu Higher Education Institutions, and the Priority Academic Program Development of Jiangsu Higher Education Institutions for financial support.

Conflicts of Interest

There are no conflicts to declare.

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