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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201701651

Link to VoR: http://dx.doi.org/10.1002/ejoc.201701651

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10.1002/ejoc.201701651

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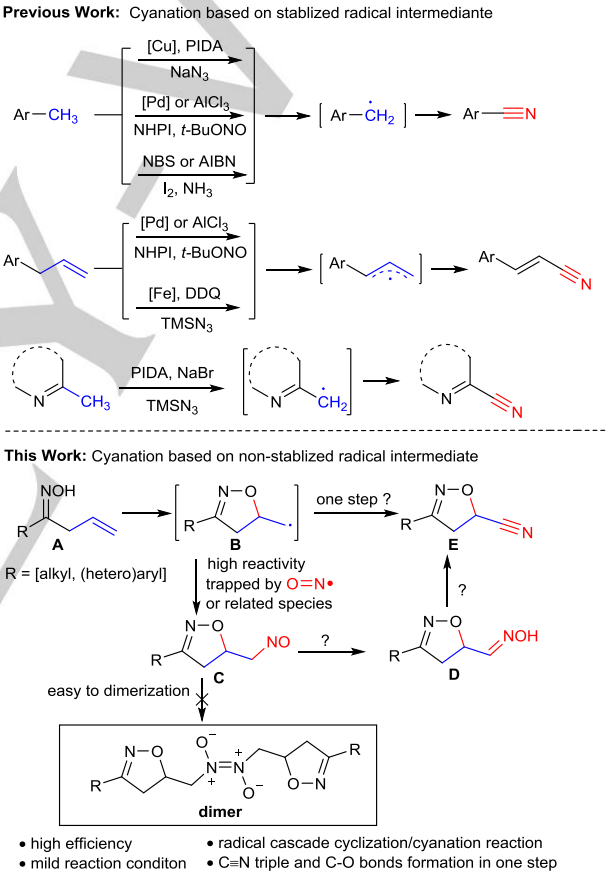
Ruthenium-catalyzed Direct Transformation of Alkenyl Oximes to 5-cyanated Isoxazolines: A Cascade Approach Based on Non-stabilized Radical Intermediate

Dan-Jun Wang, Bei-Yi Chen, Yi-Qi Wang, Xiao-Wei Zhang*[a]

Abstract: A ruthenium-catalyzed ammoxidation of alkenyl oximes under mild and neutural condtions is described. In this method, *tert*-butyl nitrite plays a dual role, acting as an oxidant as well as a nitrogen source. This reaction avoids using any toxic radical initiators or cyanide reagents. This convenient and practical method offers an easy access to 5-cyanated isoxazolines in good to high yields and shows good functional group tolerance and high efficiency. It is rather remarkable that this new reaction provides a strategically distinct approach based on non-stabilized radical intermediate and constructs C–O and C≡N triple bonds in a single-step. Moreover, the difunctionalization of unactivated olefins bearing oximes has been realized.

The nitrile group is of great importance in organic synthesis, as on one hand it is ubiquitous in numerous marketed drugs and bioactive compounds, on the other hand, it can be easily transformed to other functional groups such as amine, aldehyde, acid, amide and heterocycle.[1] Generally, the methods for the synthesis of nitriles mainly include Sandmeyer reaction,[2] Rosenmund-von Braun reaction,[3] transition-metal-catalyzed cyanation,[4] direct cyanation of C-H bonds,[5] nucleophilic aliphatic substitution,[6] and functional group transformation from corresponding alcohols, amines, amides or oximes.[7] More recently, the ammoxidation strategy for cyanation through a radical intermediate has emerged as a more efficient and economic tool for the introduction of nitrile group,[8,9,10] owing to the mild conditions and avoiding of highly toxic cyanide source. Despite great success has been made in this field by Jiao, Wang, Kang and Togo *et al.*, only substrates that can generate stabilized radical intermediate, for example, benzylic[8], allylic[9] or α-imino radicals[10], are viable for this strategy (schem 1, top). Methods that can convert other kind of radical intermediate, especially non-stabilized radical, to nitrile group are expected to extend the utility of this strategy substantially, and therefore highly desirable.

Along with the significant development of radical chemistry, radical reactions based on 1,2-difunctionalization of alkenes[11] and nitrogen-centered radical scavengers[12] or C-N bond formation with NO radical[13] have emerged as the most powerful tools for the assembly of diverse useful molecules. Meanwhile, β,γ-unsaturated ketoximes have been widely used to synthesize the isoxazolines through radical cyclization strategy,[14] since the isoxazoline skeletons are extensively found in molecules with biological activity and also act as versatile intermediates in organic synthesis.[15] A quick survey of the precedent work in this filed shows that non-stabilized radical **B** is a common intermediate involved in radical reactions of alkenyl oximes, and the existence of this functionalized alkyl radical **B** was proved both experimentally[14] and computationally.[14a,16,17]



Scheme 1. Ammoxidation strategies for cyanation based on radical intermediate

We envisioned that, an efficient one-step cyanation method could be developed if radical **B** could be selectively trapped by a nitroso radical or related species, followed by a successive tautomerization and dehydration (Scheme 1, bottom). Although trapping radical **B** with nitroso radical (or related species) and forming the dimeric compound of **C** has been reported,[14e] tuning the reaction to the desired cascade reaction pathway is still a difficult job, given the fact that the primary carbon radical **B** is extreme reactive (react with air even at low temperature)[18] and intermediate **C** is prior to dimerization.[14e] The identification

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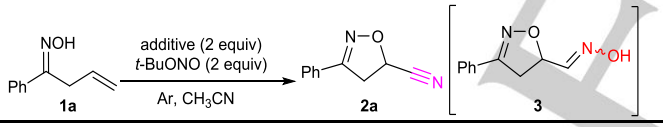
of regent compatible with the radical conditions and capable of converting the oxime **D** to nitrile is another daunting task. Herein, we report an efficient and practical ruthenium-catalyzed transformation of alkenyl oximes to 5-cyanated isoxazoline based on a non-stabilized radical intermediate.

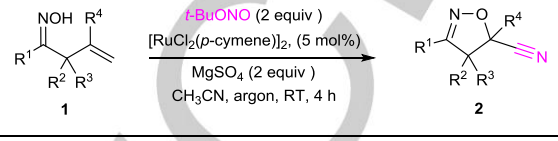
Initially, β,γ-unsaturated ketoxime **1a** was used as a model substrate for reaction condition optimization. Interestingly, when we chose *t*-BuONO as the oxidant and nitrogen source, oxime **3**, instead of the desired product **2a**, was obtained in 65% yield in the presence of 2 equivalents of LiCl in acetonitrile at 80 °C (Entry 1, Table 1). This result was unexpected since analogous Lewis acid $AlCl_3$ gave chlorinated isoxazoline as the product.[19] Encouraged by this exciting preliminary results, we subsequently screened different catalysts capable of converting oxime to nitrile, in conjunction with LiCl. When stannous chloride dihydrate was added,[20] the desired product **2a** was obtained in 49% yield (Entry 2, Table 1); however, the addition of $Zn(OTf)_2$ gave a lower yield (Entry 3, Table 1). Gratifyingly, the yield increased to 78% when 5 mol% of $[RuCl_2(p\text{-cymene})]_2$ was used as the catalyst (Entry 4, Table 1).[21] Other ruthenium catalysts, such as $Ru_3(PPh_3)_2$ and $Ru_3(CO)_{12}$, also worked for this transformation (Entries 5-6, Table 1). Surprisingly, when the reaction temperature was lowered to room temperature and the reaction time was reduced to 4 h, the yield of **2a** was almost unchanged with $[RuCl_2(p\text{-cymene})]_2$ as the catalyst (Entry 7, Table 1). Next, various additives were screened based on this mild conditions. We found many common inorganic salts were effective in this transformation,[22] with magnesium sulfate affording the best yield (Entries 8-10, Table 1). Control experiments proved that the ruthenium catalyst and additive were essential for this reaction (Entries 11-13, Table 1). Although the exact role of $MgSO_4$ is unclear at this stage, it was probably more than a water absorbing reagent, as the 4Å molecular sieve, a more effective dehydration reagent, gave lower yield (Entry 14, Table 1). When the reaction was conducted under oxygen atmosphere, the yield decreased sharply and red-brown gas was observed on the surface of the reaction solvent (Entry 15, Table 1).

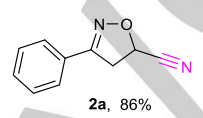
Table 1. Optimization of the conditions[a]



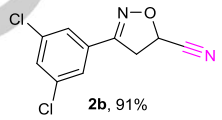
Entry	Additives	Catalyst (mol%)	Yield[b]
1[c]	LiCl	none	0%[f]
2[c]	LiCl	$SnCl_2{\cdot}2H_2O$ (50)	0%
3[c]	LiCl	$Zn(OTf)_2$ (50)	0%
4[c]	LiCl	$[RuCl_2(p\text{-cymene})]_2$ (5)	0%
5[c]	LiCl	$Ru_3(PPh_3)_2$ (5)	0%
6[c]	LiCl	$Ru_3(CO)_{12}$ (5)	43%
7[d]	LiCl	$[RuCl_2(p\text{-cymene})]_2$ (5)	66%
8[d]	CH_3CO_2Na	$[RuCl_2(p\text{-cymene})]_2$ (5)	52%
9[d]	Na_2SO_4	$[RuCl_2(p\text{-cymene})]_2$ (5)	3%
10[d]	**$MgSO_4$**	**$[RuCl_2(p\text{-cymene})]_2$ (5)**	**89 (86)%[e]**
11[d]	$MgSO_4$	$[RuCl_2(p\text{-cymene})]_2$ (2.5)	77%
12[d]	$MgSO_4$	none	0%
13[d]	none	$[RuCl_2(p\text{-cymene})]_2$ (5)	0%
14[d]	4Å MS	$[RuCl_2(p\text{-cymene})]_2$ (5)	65%
15[d,g]	$MgSO_4$	$[RuCl_2(p\text{-cymene})]_2$ (5)	14%

[a] Reaction conditions: **1a** (0.25 mmol), *t*-BuONO (0.5 mmol), additive (0.5 mmol), CH_3CN (2 mL), under argon atmosphere; [b] yield determined by ^1H NMR using MeO*t*Bu as internal standard; [c] reaction at 80 °C for 8h; [d] reaction at room temperature for 4h; [e] isolated yield was given in parenthesis. [f] **3** was isolated in 65% yield while no **2a** was obtained; [g] reaction under oxygen atmosphere. For details, see SI.

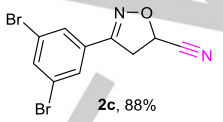




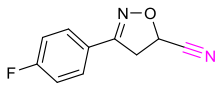
2a, 86%



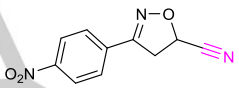
2b, 91%



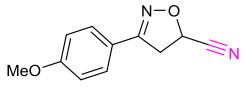
2c, 88%



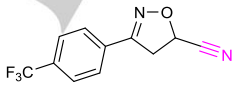
2d, 81%



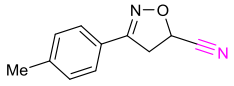
2e, 85%



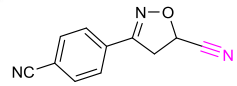
2f, 78%



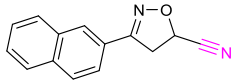
2g, 76%



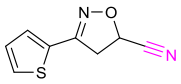
2h, 84%



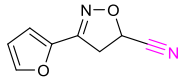
2i, 82%



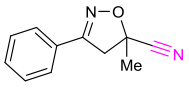
2j, 78%



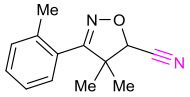
2k, 95%



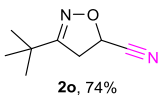
2l, 76%



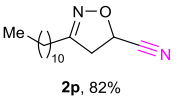
2m, 71%



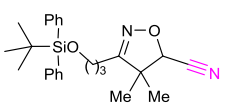
2n, 85%



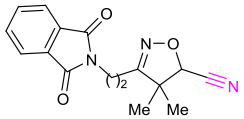
2o, 74%



2p, 82%



2q, 90%



2r, 83%

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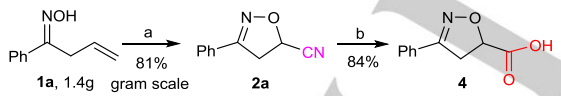
Scheme 2. Reaction scope. Reaction conditions: **1** (0.25 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (5 mol%), $MgSO_4$ (0.5 mmol), CH_3CN (2 mL), *t*-BuONO (0.5 mmol), RT, 4 h, argon atmosphere. Isolated yield. For details, see SI.

With the optimized conditions in hand (Entry 10, Table 1), we subsequently proceeded to explore the substrate scope of this radical cascade reaction. To our delight, various substrates containing aryl, heteroaryl, alkyl and other functional groups were compatible in this transformation and gave the cyanated isoxazoline in good to high yield (Scheme 2). For example, substrates bearing halide (**2b**-**2d**), nitro (**2e**), alkoxy (**2f**), trifluoromethyl (**2g**), methyl (**2i**) or cyano (**2j**) substituents on the phenyl ring, underwent the reaction well to afford the corresponding cyanation products in good to high yield (76-91%), regardless of their different electronic properties or substitution patterns. This reaction is not limited to simple benzene-based substrates, heteroaryl-substituted β,γ-unsaturated ketoximes also gave the desired products in good yields (**2j**-**2l**). Gratifyingly, the current methodology could be successfully employed to build a quaternary carbon center with specific regioselectivity (**2m**). To further investigate the substrate scope, **1n** with a quaternary carbon at C2 was next tested in our conditions, and the desired product **2n** was obtained in 85% yield. We were pleased to find that this system worked well with alkyl-substituted substrates, giving **2o** and **2p** in 74% and 82% yield, respectively. Alkyl-substituted substrates with protecting groups such as TBDPS and phthalimidyl were also tolerable in this conditions, and the desired product were obtained in high yields (**2q**, **2r**). The high yield of **2n**, **2q**, **2r** probably benefits from the Thorpe-Ingold effect.[23]

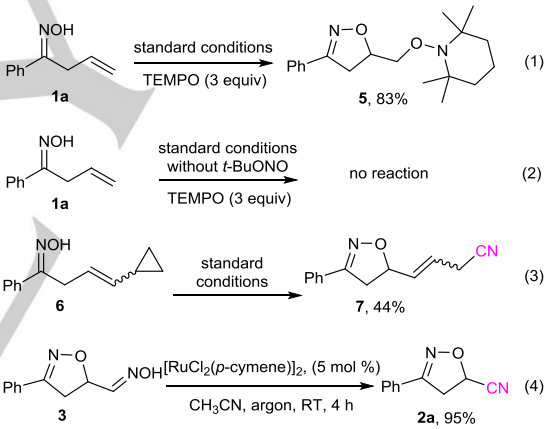
To demonstrate the utility of this reaction, transformation of **1a** was carried out on gram scale. To our delight, the desired product could be isolated in 81% yield even with lower amounts (2.5 mol%) of ruthenium catalyst. The nitrile group could be easily transformed to other useful functional groups. In this work, the carboxylic acid **4** could be prepared in 84% yield after recrystallization. This carboxyl-substituted isoxazoline could be viewed as the precursor of α-hydroxyl acid by the cleavage of N-O bond under reduction conditions.[24]



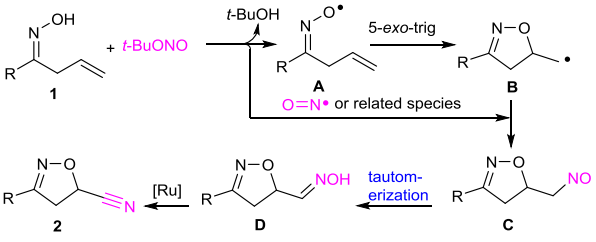
Scheme 3. Gram scale synthesis and synthetic application. [a] [$RuCl_2$(*p*-cymene)]$_2$ (2.5 mol%), $MgSO_4$ (2.0 equiv), CH_3CN, *t*-BuONO (2.0 equiv), RT, 4 h; [b] 4 N HCl aqueous solution, reflux, 10 h, recrystallized yield.

To gain insight into the mechanism, several control experiments were carried out as shown in Scheme 4. Initially, this reaction was conducted in the presence of 3 equivalents of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), the cascade reaction were completely shut down and only TEMPO-trapped product **5** was isolated in 83% yield (Eq 1). This result indicates that the cyanation reaction may proceed through a radical intermediate. Removing *t*-BuONO from above control experiment, the product **2a** or **5** could not be obtained while **1a** was totally recovered (Eq 2). This reaction implies that *t*-BuONO played the role of radical initiator in both cyanation and trapping reactions. Furthermore, radical clock experiment was also conducted to verify the reaction mechanism. When cyclopropane-substituted oxime **6** was subjected to the standard conditions, the ring opening products **7** was isolated in 44% yield (Eq 3). This result implies a radical pathway for this reaction and also supports the assumption that the C-N bond formation is not a fast process.[13a] Finally, when oxime **3** was treated with ruthenium catalyst at room temperature, nitrile **2a** was isolated in 95% yield (Eq 4). This result implies that oxime is probably the intermediate of this reaction and the function of ruthenium catalyst may be converting the oxime intermediate to nitrile.

On the basis of these preliminary results, we proposed a plausible mechanism for this transformation as depicted in Scheme 5. First, *t*-BuONO oxidized alkenyl oxime **1** to intermediate **A**, with the generation of nitroso radical and *tert*-butanol. Second, oxime radical **A** underwent a 5-*exo*-trig cyclization and generated the primary carbon radical **B**. Third, intermediate **B** combined with the nitroso radical or related species to afford the **C.** Finally, intermediate **C** tautomerized to oxime **D**, which was transformed to product **2** with the aid of ruthenium catalyst.



Scheme 4. Control experiments



Scheme 5. Proposed mechanism.

In conclusion, we have developed a radical based, mild and efficient cyanation method which converts the alkenyl oxime to the cyanated isoxazoline without using any highly toxic cyanide reagents. Various substrates bearing aryl, heteroaryl, alkyl and

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other functional groups are compatible in this transformation and give the cyanated isoxazolines in good to high yield. The key to the success is the identification of reagents combination that are compatible to each other, and at the same are able to tune the reaction to the desired pathway. The notable feature of this method is the convenient conversion of a non-stabilized alkyl radical to a nitrile group, as well as the formation of C–O and C ≡ N triple bonds in a single-step under mild and neutral conditions.

Experimental Section

General Procedure for the synthesis of cyanated isoxazolines

To a 15 mL Schlenk tube charged with $MgSO_4$ (2.0 equiv) and $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), a solution of oxime **1** (0.25 mmol) in CH_3CN (2 ml), *t*-BuONO (2.0 equiv) were added sequentially under argon atmosphere. The reaction mixture was stirred at room temperature for 4 h, then the mixture was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography.

Acknowledgements

We gratefully acknowledge the funding support of a Start-up Grant from Jiangxi Normal University.

Keywords: cyanation • olefin difunctionalization • isoxazoline • ammoxidation • radical cyclization

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10.1002/ejoc.201701651

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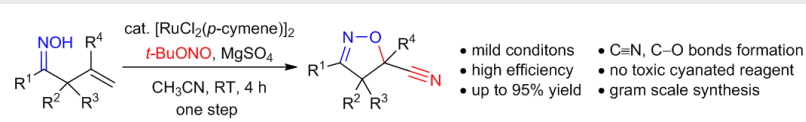

A convenient method offers an easy access to 5-cyanated isoxazolines in good to high yields and shows good functional group tolerance and high efficiency. In this protocol, *tert*-butyl nitrte plays a dual role, acting as an oxidant as well as a nitrogen source. It is rather remarkable that this new reaction avoids using any toxic radical initiator or cyanide reagents and constructs C–O and C≡N triple bonds in a single-step.

Radical ammoxidation

*Dan-Jun Wang, Bei-Yi Chen, Yi-Qi Wang, Xiao-Wei Zhang **

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Ruthenium-catalyzed Direct Transformation of Alkenyl Oximes to 5-cyanated Isoxazolines: A Cascade Approach Based on Non-stabilized Radical Intermediate

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