This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Cu-Catalyzed \( sp^3 \) C–H Bonds Oxidative Functionalization of Alkylazaarenes and Substituted Ethanones: An Efficient Approach to Isoxazoline Derivatives

Gang-Wei Wang, a,b Shi-Xia Li, a,b Quan-Xiang Wu, a and Shang-Dong Yang a,b,c

Cu-catalyzed \( sp^3 \) C–H bonds oxidative functionalization of alkylazaarenes and substituted ethanones to different kinds of isoxazoline derivatives by 1, 3-dipolar cycloaddition is reported. Cheap sources of nitro, commercially available substrates, as well as a variety of alkenes (alkynes) are applied in this transformation.

Isoxazoline derivatives display an array of significant biological properties including antiviral, antidiabetic, antitubulin, as well as antineoplastic activity. [1] Currently, drugs containing the isoxazoline moiety have already been used in common clinical treatment, and some representative molecules are shown in Scheme 1. [2] Meanwhile, isoxazoline derivatives are useful ligands [3] and valuable synthetic intermediates for the construction of 1,3-diketones, \( \beta \)-hydroxyketones, and \( \gamma \)-amino alcohols. [4] As a result, great efforts have been devoted in order to develop synthetic methods for isoxazoline derivatives during the past century. [5] The classic, well-established approach of 1,3-dipolar cycloaddition of dipolarophiles with nitrile oxides has shown great advances in the synthesis of isoxazolines. However, as the nitrile oxides need to be prepared in situ from specific substrates, such as hydroximinoyl chlorides, aldoximes, and primary nitro compounds with certain reagents, the development of alternative methods for the formation of nitrile oxides from stable, cheap, and readily accessible precursors as well as identifying convenient catalytic systems is still particularly challenging and highly attractive.

Expanding the applicability and exploring simple catalytic systems for metal-catalyzed \( sp^3 \) C–H bond functionalizations have been ambitious goals for chemists during the past decade. [6] Among them, the metal-catalyzed \( sp^3 \) C–H bond nitration reaction is still an unresolved task. [7] Herein, we used Cu-catalyzed \( sp^3 \) C–H bond nitration to form the nitrile oxides and subsequently to go through 1,3-dipolar cycloadditions with alkenes or alkynes in order to obtain isoxazoline derivatives. The \( sp^3 \) C–H bonds of the methylazaarenes and substituted ethanones were successfully converted into the oxidative products combined with various alkenes. Generally, by using a cheap nitro source (KNO₃) and commercially available substrates, this method provided an efficient and concise approach to isoxazoline derivatives, which might possess great potential applications in the design of ligands as well as in tests of biological activity (Scheme 1).

Scheme 1. Cu-catalyzed different types of \( sp^3 \) C–H bonds oxidative functionalization to synthesis isoxazolines.

Metal-catalyzed oxidation of the benzylic \( sp^3 \) C–H bond of the methylazaarenes has stimulated great research efforts during the last decade, [8] so we chose 2-methylquinoline 1a as the standard substrate to react with allylbenzene 2a in order to perform this \( sp^3 \) C–H oxidative functionalization reaction. After a series of screens on different catalysts, oxidants, solvents, and nitro sources, we settled...
on the following reaction conditions: 10 mol % of CuCl as catalysts, 2 equiv of $K_2S_2O_8$ as oxidant, 4 equiv of $KNO_3$ as nitro source, and DMAc as a solvent at 100 °C for 12 h under air atmosphere. The desired 1, 3-dipolar cycloaddition product $3\text{a}$ was obtained in 82% yield combined with a trace amount of quinoline-2-carbaldehyde as the byproduct (see Supporting Information).

**Table 1.** Substrate scope: methyl azazulenes, alkenes and alkynes. $^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield [%]$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>$R^1 = ClPh$</td>
<td>82</td>
</tr>
<tr>
<td>3b</td>
<td>$R^1 = ClC_6H_4$</td>
<td>80</td>
</tr>
<tr>
<td>3c</td>
<td>$R^1 = ClCH$</td>
<td>81</td>
</tr>
<tr>
<td>3d</td>
<td>$R^1 = CHCl$</td>
<td>52</td>
</tr>
<tr>
<td>2e</td>
<td>$R^1 = CN$</td>
<td>74</td>
</tr>
<tr>
<td>2f</td>
<td>$R^1 = CO2Et$</td>
<td>77</td>
</tr>
<tr>
<td>2g</td>
<td>$R^1 = SO2Ph$</td>
<td>66</td>
</tr>
<tr>
<td>2h</td>
<td>$R^1 = PO(Ph)$</td>
<td>82</td>
</tr>
<tr>
<td>2i</td>
<td>$R^1 = Ph$</td>
<td>trace</td>
</tr>
</tbody>
</table>

$^a$ Reaction was carried out with CuCl (10 mol %), $K_2S_2O_8$ (2.0 equiv), $KNO_3$ (4.0 equiv), 2-methyl azazulenes (0.30 mmol), alkenes or alkynes (0.9 mmol) in DMAc (3.0 mL) at 100 °C for 12 h under air. $^b$ Isolated yield. $^c$ All the reaction systems produced trace amounts of corresponding quinoline-2-carbaldehyde as byproduct. $^d$ Mixed with trace amount of impurities.

With optimized conditions in hand, we explored the substrate scope. First, a variety of alkenes were tested. In general, all these terminal alkenes with either electron-donating or electron-withdrawing substituents afforded the corresponding isoxazoline products in moderate to excellent yields (Table 1). For example, alkenes bearing useful functional groups, such as free alcohol, cyano, ester, phenylsulfanyl, and nitro led to the desired product in moderate to good yields ($3c$, $3g$, $3h$, $3i$, $3l$). Diphenyl(vinyl)phosphine oxide produced the product in an excellent yield of 92% ($3j$). Aliphatic alkenes were shown to be compatible with the optimized conditions ($3a$, $3c$, $3d$, $3o$, $3p$). When styrene was applied in the reaction, only a trace amount of product was achieved ($3k$). Besides terminal alkenes, a cycloolefin was also a suitable substrate, although a low yield was achieved ($3n$). Next, substituted 2-methylquinoline was tested, wherein electronically disparate substituents on the aromatic ring had limited influence on the reaction process, and the corresponding products were obtained in moderate to good yields ($3q$-$3u$). We also used 3-methylquinoline and 4-methylquinoline as substrates to perform this reaction, however, 3-methylquinoline could only provide a trace amount of desired product and 4-methylquinoline failed to provide any corresponding product. Different 2-methyl azazulenes were also applied into the catalytic system, and 2-methylbenzo/[f]quinoline, 2-methylquinolina, 1-methylsiquioxane, and substituted benzoxazinones all gave the desired product in moderate to good yields ($3v$-$3z$), but 2-methylpyridine failed to give the desired product. An alkyne also served as a good dipolarophile under this catalytic system and 1-heptyne provided the desired product in 71% yield ($3aa$). But phenylacetylene was not a suitable substrate for this transformation. When 2-ethylquinoline was used as substrate under the standard condition, a cascade $sp^3$ C–H bond oxidative functionalization was achieved to access the different isoxazoline derivatives.$^{[9]}$

**Table 2.** Substrates scope: acetoephone. $^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Alkene or Alkyne</th>
<th>Product</th>
<th>Yield [%]$^p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>$R^2 = 4-Cl$</td>
<td>$R^1 = Ph$</td>
<td>5a</td>
<td>23%$^c$</td>
</tr>
<tr>
<td>4b</td>
<td>$R^2 = 4-CN$</td>
<td>$R^1 = Ph$</td>
<td>5b</td>
<td>53%</td>
</tr>
<tr>
<td>4c</td>
<td>$R^2 = 4-F$</td>
<td>$R^1 = Ph$</td>
<td>5c</td>
<td>50%$^b$</td>
</tr>
<tr>
<td>4d</td>
<td>$R^2 = 4-NO_2$</td>
<td>$R^1 = Ph$</td>
<td>5d</td>
<td>63%</td>
</tr>
<tr>
<td>4e</td>
<td>$R^2 = 4-OMe$</td>
<td>$R^1 = Ph$</td>
<td>5e</td>
<td>trace</td>
</tr>
<tr>
<td>4f</td>
<td>$R^2 = 2-F$</td>
<td>$R^1 = Ph$</td>
<td>5f</td>
<td>27%</td>
</tr>
<tr>
<td>4g</td>
<td>$R^2 = 4-OMe$</td>
<td>$R^1 = Ph$</td>
<td>5g</td>
<td>67%</td>
</tr>
<tr>
<td>4h</td>
<td>$R^2 = 4-OMe$</td>
<td>$R^1 = Ph$</td>
<td>5h</td>
<td>62%</td>
</tr>
</tbody>
</table>

$^a$ The reaction was carried out with Cu(acac)$_2$ (10 mol %), $K_2S_2O_8$ (6.0 equiv), $KNO_3$ (4.0 equiv), acetoephone (0.30 mmol), alkenes or alkynes (0.9 mmol) in DMAc (3.0 mL) at 100 °C for 12 h under air. $^b$ Isolated yield. $^c$ Mixed with trace amount of impurities.

a) Radical trapping experiment

b) Oxidative dimerization reaction of 1a

**Scheme 2.** Control experiments
The functionalization of the α-C–H bond of carbonyl compounds has long been valued as a fundamental transformation in organic chemistry. Based on this transformation, Horiuchi and Roy developed approaches to isoxazolines by using acetone (or acetonitrile) as substrate and solvent combined with iron salts or ammonium cerium nitrate (CAN). These achievements, however elegant, could only provide a limited substrate scope. Different acetonaphthones were therefore tested in order to test the applicability of our transformation. We found that with a slightly changed catalytic system, acetonaphthones with electron-withdrawing groups substituted on the aromatic ring could provide corresponding products in low to moderate yields, and a higher yield was achieved for more electron-deficient substrates (Table 2, 5a-5f). When 1-(quinolin-2-yl) ethanone was used as substrates, 5g and 5h were formed in 67% and 62% yield, respectively. Other ketones, propiophenone and acetone for example, failed to give the desired product.

To gain insight into the mechanism, several control experiments were carried out by using 2-methylquinoline 1a as substrate (Scheme 2). When a radical scavenger, 1-diphenylpropylene (1 equiv) was added into the reaction, the desired product was not observed at all, but AA and BB were produced in yields of 29% and 14%, respectively. This result implied that the reaction might involve generation of a nitro radical and oxygen. When 1a was applied to the reaction system in the absence of alkenes or alkyynes, oxadiazole CC was achieved in a 24% yield. This result indicates that nitride oxide could be the key intermediate for this reaction. 5o

**Scheme 3. Proposed mechanism**

On the basis of the above results and previous literature, we proposed a tentative pathway for this transformation (Scheme 3). Decomposition of the potassium peroxysulphate may initially occur in order to generate the sulfate radical anion, which subsequently reacted with KNO3 in order to form a nitrogen dioxide radical as well as oxygen. 13d-4) Meanwhile, 1a reacted with CuCl to produce the active metal enamide species A 14 and A was attacked by NO2 radical in order to obtain the intermediate B, which provided the nitride oxide C through the processes of oxidation and dehydration 13d,e). The nitride oxide C then reacted with alkenes or alkyynes through 1, 3-dipolar cycloaddition reaction, and the final isoxazolines 3 were achieved. 5o At the same time, 1a could also be converted into a radical intermediate A through a single electron transfer (SET) process 13d then A reacted with oxygen to provide the byproduct quinoline-2-carbaldehyde in a trace amount (see Supporting Information). 12 When substituted acetonaphthone 4 was used to provide the corresponding isoxazoline derivatives 5, a similar mechanism could be applied (active metal enol species was formed instead of enamide species A) in the reaction course.

**Conclusions**

In conclusion, by using Cu-catalyzed sp3 C–H bond nitration to generate the nitrile oxides in situ and subsequently go through 1, 3-dipolar cycloaddition with alkenes or alkyynes, we developed an efficient and concise approach to isoxazoline derivatives. When an inexpensive nitro source (KNO3) and commercially available substrates are the starting point, the sp3 C–H bonds of methylnitroarenes and substituted ethanones can be successfully functionalized with the assistance of different alkenes and alkyynes. Current work is ongoing toward the application of these isoxazoline derivatives to biological activity tests.

**Acknowledgement**

We are grateful for the NSFC (Nos. 21272100 and 21202075) and Program for New Century Excellent Talents in University (NCET-11-0215 and lzujbky-2013-k07) financial support. S.F. Reichard contributed editing.

**Notes and references**

a State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China. E-mail: yangshd@lzu.edu.cn; Fax: +86-931-8912859; Tel: +86-931-8912859.

b State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Lanzhou 730000, P. R. China.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI:10.1039/c000000x


Examples on metal-catalyzed benzylic C–H oxidation see: (a) A. J. Catino, J. M. Nichols, H. Choi, S. Gottipamula and M. P. Doyle, 
*Org. Lett.* 2005, 7, 5167; (b) Y. Bonvin, E. Callens, I. Larrosa, D. A. 
Lett.* 2011, 13, 1567; (e) B. Qian, P. Xie, Y. Xie and H. Huang, *Org. 
Lett.* 2011, 13, 2580; (f) Y. Yan, K. Xu, Y. Fang and Z. Wang, *J. 
Org. Chem.* 2011, 76, 6849; (g) Z.-Q. Wang, W.-W. Zhang, L.-B. Gong, 
2011, 50, 8968; (h) J. D. Houwer, K. A. Tehrani and B. U. W. Maes, 
48, 11993; (j) Y. Li, F. Guo, Z. Zha and Z. Yang, *Chem. Asian J.* 
2013, 8, 534; (k) Y.-G. Zhang, J.-K. Xu, X.-M. Li and S.-K. Tian, 

DOI:10.1039/C5CC01004G

For recent reviews, see: (a) D. A. Culkin and J. F. Hartwig, *Acc. 
2009, 110, 1082; (c) A. C. B. Burtoloso, *Synlett* 2009, 320; (d) C. C. 
(e) T. Anker, C. C. Cosner and P. Helquist, *Chem.-Eur. J.* 2013, 19, 
1858 

(a) K.-I. Itoh and C. A. Horiuichi, *Tetrahedron* 2004, 60, 1671; (b) K.- 
Horiuichi, *Synthesis* 2005, 20, 3541; (c) S. Béha, D. Giguère, R. 

(a) S. Hirashima, Y. Kudo, T. Nobuta, N. Tada and A. Itoh, 
*Tetrahedron Lett.* 2009, 50, 4328; (b) S. Maity, S. Manu, S. Rana, T. 

77, 7665; (b) S. Maity, S. Maity, S. Rana, S. Agasti and D. Maity, *Org. 
Lett.* 2012, 14, 1736; (c) Y.-M. Li, X.-H. Wei, X.-A. Li and S.-D. 
Yang, *Chem. Commun.*, 2013, 49, 11701; (d) Y. Liu, B. Jiang, W. 
Zhang and Z. Xu, *J. Org. Chem.* 2013, 78, 966; (e) Y.-K. Liu, S.-J. 
1997 

B. Qian, S. Guo, J. Shao, Q. Zhu, L. Yang, C. Xia and H. Huang, *J. 