Copper-Mediated Oxidative C–H/N–H Activations with Alkynes by Removable Hydrazides

Feng Xiong¹, Bo Li², Chenrui Yang¹, Liang Zou¹, Wenbo Ma², Linghui Gu*², Ruhuai Mei*¹,², and Lutz Ackermann*³,⁴

Address: ¹ Key Laboratory of Coarse Cereal Processing, Ministry of Agriculture and Rural Affairs, College of Food and Biological Engineering, Chengdu University, Chengdu 610106, P. R. China.
² Antibiotics Research and Re-evaluation Key Laboratory of Sichuan Province, Sichuan Industrial Institute of Antibiotics, Chengdu University, P.R. China, 610052.
³ Institut für Organische und Biomolekulare Chemie, Georg-August-Universität, Tammannstraße 2, 37077 Göttingen, Germany.
⁴ Wöhler Research Institute for Sustainable Chemistry (WISCh), Georg-August-Universität Göttingen, Tammannstraße 2, 37077 Göttingen, Germany.

Email: Linghui Gu - cdglh017@163.com
Ruhuai Mei - rmei@cdu.edu.cn
Lutz Ackermann - lutz.ackermann@chemie.uni-goettingen.de.

* Corresponding author

Abstract

The efficient copper-mediated oxidative C–H alkynylaiton of benzhydrazides was accomplished with terminal alkynes. Thus, a hetero-aromatic removable N-2-
pyridylhydrazide allowed for domino C–H/N–H functionalization. The approach featured remarkable functional group compatibility and ample substrates scope. Thereby, highly functionalized aromatic and hetero-aromatic isoindolin-1-ones were accessed with high efficacy with rate-limiting C–H cleavage.

Keywords
copper; benzhydrazides; 3-methyleneisoindolin-1-one; removable directing group

Introduction

Inexpensive copper-promoted oxidative C−H activations [1-11] have been recognized as competent tools for the efficient assembly and late-stage functionalization of organic molecular due to its natural abundance and versatile reactivity. Early examples of copper-promoted C−H activation of 2-arylpuridines were disclosed by Yu [12] and Chatani [13] independently. Inspired by these studies, various copper-induced C−H functionalizations, such as arylation, alkynylation, cyanation, amination, nitration, oxygenation, thiolation, halogenation and phosphorylation among others, were accomplished [14-19].

The 3-methyleneisoindolin-1-one moiety represents key structure motif in natural products [20-23] or important pharmacophores [24]. In this context, You [25], Huang [26], Liu [27] and Jack Li [28] elegantly disclosed copper-mediated/catalyzed cascade C–H alkynylation and annulation with terminal alkyne to afford 3-methyleneisoindolinone derivatives, through the assistance of 8-aminoquinoline [29] or 2-aminoaryl-1H-pyrazole [30] auxiliaries (Figure 1a). Besides, the cobalt(II) [31] or nickel(II) [32, 33] catalyzed, pyridine oxide (PyO) directed tandem alkynylation/annulation were realized by Niu and Song, which also provided the 3-
methylenisoindolin-1-one scaffolds (Figure 1b). Notably, a sustainable cupraelectrocatalyzed alkyne annulation was very recently achieved by Ackermann, which gave rapid access to synthetically meaningful isoindolones (Figure 1c) [34]. In spite of these indisputable advances, the successful removal of the directing groups to deliver the NH-free 3-methylenisoindolin-1-one has thus far unfortunately proven elusive [35].

Previous studies:

![chemical structures](image)

(a) 

(b) 

(c) 

This work:

(d) 

**Figure 1:** Assembly of 3-methylenisoindolin-1-one via 3d transition metal-mediated/catalyzed oxidative C−H/N−H activation.

2-(1-Methylhydrazinyl)pyridine (MHP) [36], was identified as a powerful removable bidentate directing group, which found widespread application in various cobalt catalyzed C−H activations [37-40]. Thus, our group also accomplished a set of electrochemical cobalt-catalyzed C−H activations with the MHP auxiliary [41-44]. In continuation of studies on sustainable 3d transition metal-catalyzed C−H activation [41-49], we have now discovered a robust copper-promoted oxidative C−H/N−H
functionalization with terminal alkynes (Figure 1d). Notable advantages of our protocol includes: 1) removable N-2-pyridylhydrazides (MHP) auxiliary used for copper-mediated oxidative C–H activations, 2) excellent functional group tolerance, compatibility with valuable heterocycles and 3) mechanistic studies toward copper-mediated oxidative C–H alkynylations.

**Results and Discussion**

We initiated our investigation by utilizing benzhydrazide 1a and ethynylbenzene 2a as the standard substrates (Table 1). After preliminary solvent optimization, we discovered that the desired *ortho*-selective C–H activation occurred efficiently by the treatment of hydrazide 1a with terminal alkyne 2a and stoichiometric amount of Cu(OAc)$_2$ in DMSO (entries 1-3). Reaction optimization revealed that the most appropriate temperature was 90 °C (entries 3-6). An evaluation of bases showed that Na$_2$CO$_3$ was optimal (entries 7-11). The best result was obtained when Cu(OAc)$_2$ (1.3 equiv) was utilized in DMSO (6.0 mL) (entries 12-14). A similar result was obtained when Cu(OAc)$_2$$	ext{•}$H$_2$O was used instead of Cu(OAc)$_2$ (entry 15). Only trace amount of product 3aa was observed in the absence of either Cu(OAc)$_2$ or Na$_2$CO$_3$ (entries 16-17). When the reaction was performed under a nitrogen atmosphere, the efficacy was significantly decreased (entry 18).

<table>
<thead>
<tr>
<th>Table 1: Optimization of copper-mediated C–H/N–H functionalization with terminal alkynes 2a.ª</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>base</th>
<th>temp. (°C)</th>
<th>Z/E</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>Na₂CO₃</td>
<td>90</td>
<td>---</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>NMP</td>
<td>Na₂CO₃</td>
<td>90</td>
<td>---</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>DMSO</td>
<td>Na₂CO₃</td>
<td>90</td>
<td>12/1</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>DMSO</td>
<td>Na₂CO₃</td>
<td>110</td>
<td>8/1</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>DMSO</td>
<td>Na₂CO₃</td>
<td>80</td>
<td>15/1</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>DMSO</td>
<td>Na₂CO₃</td>
<td>60</td>
<td>---</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>DMSO</td>
<td>NaOAc</td>
<td>90</td>
<td>---</td>
<td>25</td>
</tr>
<tr>
<td>8</td>
<td>DMSO</td>
<td>NaOPiv</td>
<td>90</td>
<td>---</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>DMSO</td>
<td>K₂CO₃</td>
<td>90</td>
<td>18/1</td>
<td>58</td>
</tr>
<tr>
<td>10</td>
<td>DMSO</td>
<td>Cs₂CO₃</td>
<td>90</td>
<td>20/1</td>
<td>44</td>
</tr>
<tr>
<td>11</td>
<td>DMSO</td>
<td>DBU</td>
<td>90</td>
<td>---</td>
<td>13</td>
</tr>
<tr>
<td>12ᵇ</td>
<td>DMSO</td>
<td>Na₂CO₃</td>
<td>90</td>
<td>12/1</td>
<td>42</td>
</tr>
<tr>
<td>13ᶜ</td>
<td>DMSO</td>
<td>Na₂CO₃</td>
<td>90</td>
<td>9/1</td>
<td>83</td>
</tr>
<tr>
<td>14ᶜᵈ</td>
<td>DMSO</td>
<td>Na₂CO₃</td>
<td>90</td>
<td>13/1</td>
<td>89</td>
</tr>
<tr>
<td>15ᶜᵈᵉ</td>
<td>DMSO</td>
<td>Na₂CO₃</td>
<td>90</td>
<td>12/1</td>
<td>86</td>
</tr>
<tr>
<td>16</td>
<td>DMSO</td>
<td>---</td>
<td>90</td>
<td>---</td>
<td>trace</td>
</tr>
<tr>
<td>17ᶠ</td>
<td>DMSO</td>
<td>Na₂CO₃</td>
<td>90</td>
<td>---</td>
<td>trace</td>
</tr>
<tr>
<td>18ᵍ</td>
<td>DMSO</td>
<td>Na₂CO₃</td>
<td>90</td>
<td>---</td>
<td>37</td>
</tr>
</tbody>
</table>

* Reaction conditions: 1a (0.30 mmol), 2a (0.90 mmol), Cu(OAc)₂ (1.1 equiv), base (2.0 equiv), solvent (3.0 mL), 15 h, under air. ᵇ Cu(OAc)₂ (0.8 equiv). ᵇ Cu(OAc)₂ (1.3 equiv).
equiv).\textsuperscript{d} DMSO (6.0 mL). \textsuperscript{e} Cu(OAc)\textsubscript{2}•H\textsubscript{2}O (1.3 equiv). \textsuperscript{f} Without Cu(OAc)\textsubscript{2}. g Under N\textsubscript{2}.

We next examined the versatility of the copper-promoted ethynylbenzene 2a annulation with various benzhydrazides 1 under the optimized reaction conditions (Scheme 1). To our delight, hydrazides 1 with electron-donating or electron-withdrawing substituents were efficiently converted within the C–H/N–H activation annulation process. Notably, a wide range of valuable electrophilic functional groups, such as halogen, methylthio, cyano, amino and ester, were well compatible, which should prove instrumental for the further diversification of the thus-obtained 3-methyleneisoindolin-1-one 3da-3ka. For substrates bearing two potential reactive sites, the annulation selectively took place at the less congested ortho-C–H bond (3la, 3ma). Moreover, the challenging isonicotinic acid hydrazide 1n was also amenable to this protocol and delivered the desired product 3na with high regio-selectivity.
Scheme 1. Copper-mediated oxidative C–H/N–H functionalization of hydrazides 1 with ethynylbenzene 2a.

We further investigated the viable scope of differently substituted terminal alkynes 2 as the general coupling partners for this transformation. As showed in Scheme 2, a
variety of valuable electrophilic substitutes were well tolerated. Moreover, substrate with a highly reactive unprotected amino group also delivered the corresponding product 3cn with good yield. The robustness of this protocol was further highlighted by the excellent reactivity of heterocyclic acetylenes (2p-2r).

Our copper-promoted C−H annulation protocol was not restricted to terminal alkynes. Under identical reaction conditions, commercially available alkynyl carboxylic acids 4 also proved to be a viable substrate. Thus, the corresponding isoindolone 3aa was assembled via a tandem decarboxylative C−H/C−C sequence (Scheme 3a). The practical relevance of our approach was reflected by the cleavage of N-2-pyridylhydrazides group (Scheme 3b).
Scheme 2: Copper-mediated oxidative C–H/N–H functionalization of with alkynes 2

(a) Copper-mediated decarboxylative C–H/N–H annulaiton

\[
\begin{array}{c}
\text{O} \\
\text{Me} \\
\text{N} \quad \text{N} \\
\text{H} \\
\text{Ph}
\end{array}
\begin{array}{c}
\text{CO}_2\text{H} \\
\text{Cu(OAc)}_2 (1.3 \text{ equiv}) \\
\text{Na}_2\text{CO}_3 (2.0 \text{ equiv}) \\
\text{DMSO, air} \\
15 \text{ h}, 90 \text{ °C}
\end{array}
\begin{array}{c}
\text{O} \\
\text{Me} \\
\text{N} \quad \text{N} \\
\text{Ph} \\
\text{Py}
\end{array}
\]

\[1a + 4 \rightarrow 3aa, 63\%, Z/E = 27/1\]

(b) Removal of the directing group

\[
\begin{array}{c}
\text{O} \\
\text{Me} \\
\text{N} \quad \text{N} \\
\text{Ph} \\
\text{Py}
\end{array}
\begin{array}{c}
\text{Sml}_2 (10 \text{ equiv}) \\
\text{THF} \\
48 \text{ h}, 23 \text{ °C}
\end{array}
\begin{array}{c}
\text{O} \\
\text{Me} \\
\text{N} \\
\text{H} \\
\text{Ph}
\end{array}
\]

\[3\text{aa} \rightarrow \text{S-3aa}, 79\%, Z/E = 4/1\]

Scheme 3: Decarboxylative C–H/N–H activation and cleavage of the directing group

Inspired by the remarkable robustness of the copper-promoted C–H activations with alkynes, we became interested to explore its working mode by a set of experiments. To this end, electron-poor arenes inherently reacted preferentially in intermolecular competition experiments (Scheme 4a). This observation could be explained in terms of a concerted metalation deprotonation (CMD) mechanism [50]. Interestingly, electron-rich alkyne 2f displayed a higher reactivity in the copper promoted C–H activations as compared to their electron-poor analog (Scheme 4b). A significant H/D scrambling was not detected in the ortho-position of the re-isolated benzhydrazide 1c and product 3ca, when the reaction was conducted with the isotopically labelled D_2O as co-solvent (Scheme 4c). This observation indicated the C–H cleavage is irreversible. In accordance with this finding, a kinetic isotope effect (KIE) of \( k_\text{H}/k_\text{D} \approx 6.1 \) was observed by parallel experiments, again suggesting that the C–H activation is kinetically relevant (Scheme 4d).
Based on our mechanistic findings and previous studies, we propose a tentative plausible reaction pathway in Scheme 5. The transformation commences with substrate coordination and subsequent carboxylate-assisted C–H cleavage to deliver copper(II) intermediate A. Next, the copper(III) carboxylate species B is generated. Thereafter, a facile base assisted ligand exchange which was followed by reductive...
elimination affords the alkynylated benzamide D. Finally, the desired isoindolone 3 is formed via an intramolecular hydroamination in the presence of base.

![Scheme 5: Proposed reaction pathway.](image)

**Conclusion**

In conclusion, we have reported on the chelation-assisted oxidative copper-promoted cascade C–H alkynylation and intramolecular annulation. The removable N-2-pyridylhydrazide was utilized to facilitate copper(II)-promoted C–H activations. Thus, the robust copper-mediated C–H activation featured remarkable compatibility of synthetically meaningful functional groups, giving facile access to valuable 3-methyleneisoindolin-1-one scaffolds.
Experimental

General information

Yields refer to isolated compounds, estimated to be > 95% pure as determined by $^1$H-NMR. Chromatography separations were carried out on silica gel 60H (200-300 mesh) manufactured by Qingdao Haiyang Chemical Group Co. (China). High resolution mass spectrometry (HRMS) was measured on Thermo-DFS mass spectrometer. NMR spectra were recorded on JEOL 600 NMR ($^1$H 600 MHz; $^{13}$C 150 MHz; $^{19}$F 565 MHz) in CDCl$_3$. If not otherwise specified, chemical shifts (δ) are given in ppm.

Materials

Reactions were carried out under an Argon atmosphere using pre–dried glassware, if not noted otherwise. Benzhydrazides 1 were synthesized according to a previously described method [36, 44]. Other chemicals were obtained from commercial sources and were used without further purification.

General Procedure for the Copper-Promoted Oxidative C–H/N–H Activation with alkynes.

To a 25 mL schlenk tube was added benzhydrazide 1 (0.30 mmol, 1.00 equiv), alkyne (0.90 mmol, 3.0 equiv), Cu(OAc)$_2$ (71 mg, 0.39 mmol, 1.30 equiv) and Na$_2$CO$_3$ (64 mg, 0.60 mmol, 2.00 equiv) under an air atmosphere. The mixture was stirred at 90 °C for 15 h. At ambient temperature, H$_2$O (15 mL) and Et$_3$N (0.5 mL) were added and a suspension was formed immediately. After filtrated through a celite pad, the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic phase
was washed with brine (20 mL) and dried over Na₂SO₄. Then Et₃N (0.5 mL), silica gel (0.8 g) were added and the combined solvent was removed under reduced pressure. The residue solid sample was purified by column chromatography on silica gel (petroleum/EtOAc = 5/1 to 2/1, with 1% Et₃N) yielded the desired product 3.

(Z)-3-Benzylidene-2-(methyl[pyridin-2-yl]amino)isoindolin-1-one (3aa): The general procedure was followed using hydrazide 1a (68.2 mg, 0.30 mmol) and alkyne 2a (91.9 mg, 0.90 mmol). Purification by column chromatography on silica gel (petroleum/EtOAc 20/1, with 1% Et₃N) yielded 3aa (87.4 mg, 89%, Z/E = 13:1) as a light yellow solid. M. p.: 67–68 °C. ¹H NMR (600 MHz, CDCl₃) δ = 8.13 (ddd, J = 5.0, 1.9, 0.9 Hz, 1H), 7.90 (dd, J = 7.6, 1.0 Hz, 1H), 7.85–7.82 (m, 1H), 7.70 (d, J = 1.2 Hz, 1H), 7.56 (dd, J = 7.6, 0.9 Hz, 1H), 7.44 (ddd, J = 8.8, 7.1, 1.9 Hz, 1H), 7.17–7.05 (m, 5H), 6.85 (d, J = 0.9 Hz, 1H), 6.67 (ddd, J = 7.2, 5.0, 0.9 Hz, 1H), 6.44–6.41 (m, 1H), 3.01 (s, 3H). ¹³C{¹H} NMR (150 MHz, CDCl₃) δ = 165.7 (Cq), 157.6 (Cq), 147.7 (CH), 137.4 (CH), 136.2 (Cq), 133.2 (Cq), 132.8 (CH), 132.1 (Cq), 129.3 (CH), 128.7 (CH), 127.3 (CH), 127.3 (CH), 126.5 (Cq), 123.8 (CH), 119.8 (CH), 114.3 (CH), 107.8 (CH), 106.4 (CH), 36.7 (CH₃). HR-MS (ESI) m/z calcd for C₂₁H₁₈N₃O [M+H⁺] 328.1444, found 328.1439.

Supporting Information

Supporting Information File 1:
Characterization data for 3 and copies of ¹H, ¹³C, and ¹⁹F NMR spectra.

ORCID® iDs

Wenbo Ma - https://orcid.org/0000-0002-9690-3639
Acknowledgements

Generous Support by National Natural Science Foundation of China (Grant No. 21901023), “Thousand Talents Program” of Sichuan Province (R. Mei) and the DFG (Gottfried-Wilhelm-Leibniz award to L.A.) is gratefully acknowledged.

References