Copper-catalyzed CuAAC/intramolecular C–H arylation sequence: Synthesis of annulated 1,2,3-triazoles

Rajkumar Jeyachandran¹, Harish Kumar Potukuchi¹,² and Lutz Ackermann*¹

Abstract
Step-economical syntheses of annulated 1,2,3-triazoles were accomplished through copper-catalyzed intramolecular direct arylations in sustainable one-pot reactions. Thus, catalyzed cascade reactions involving [3 + 2]-azide–alkyne cycloadditions (CuAAC) and C–H bond functionalizations provided direct access to fully substituted 1,2,3-triazoles with excellent chemo- and regioselectivities. Likewise, the optimized catalytic system proved applicable to the direct preparation of 1,2-diarylated azoles through a one-pot C–H/N–H arylation reaction.

Introduction
Transition-metal-catalyzed C–H bond functionalizations are increasingly viable tools for step-economical syntheses of various valuable bioactive compounds [1-3], which avoid the preparation and use of preactivated substrates [4-16]. This streamlining of organic synthesis has predominantly been accomplished with palladium [4-16], rhodium [17-19] or ruthenium [20-22] complexes [4-16]. However, less expensive nickel, cobalt, iron or copper catalysts bear great potential for the development of economically attractive transformations [23-50]. In this context, we previously reported on the use of cost-effective copper(I) catalysts for direct arylations of 1,2,3-triazoles. Thus, we showed that intermolecular copper-catalyzed C–H bond functionalizations could be combined with the Huisgen [51] copper(I)-catalyzed [52,53] [3 + 2]-azide–alkyne cycloaddition (CuAAC) [54], while C–H bond arylations of 1,2,3-triazoles were previously only accomplished with more expensive palladium [55-62] or ruthenium [63-66] catalysts. Notably, this strategy allowed for the atom-economical synthesis of fully substituted 1,2,3-triazoles in a highly regioselective fashion [54,67]. While the research groups of Rutjes [68] as well as Sharpless [69] elegantly devised alternative approaches exploiting 1-haloalkynes [70], we became interested in exploring a single [71-73] inexpensive copper catalyst for one-pot reaction sequences comprising a 1,3-dipolar cycloaddition
along with an intramolecular C–H bond arylation; in particular, because of the notable biological activities exerted by fully substituted 1,2,3-triazoles [74-88]. As a consequence, we wish to present herein novel cascade reactions, in which cost-effective copper(I) compounds serve as the catalyst for two mechanistically distinct transformations for the synthesis of fully substituted annulated 1,2,3-triazoles as well as for twofold N–H/C–H bond arylations. Notable features of our strategy include (i) the development of a chemoselective C–H arylation-based three-component reaction, as well as (ii) the use of inexpensive CuI for the formation of up to one C–C and three C–N bonds in a site-selective fashion (Scheme 1).

### Results and Discussion

We initiated our studies by exploring reaction conditions for the key copper-catalyzed intramolecular direct C–H bond arylation, employing substrate 3a (Table 1). Notably, the envisioned C–H bond functionalization occurred readily with the aryl iodide 3a when catalytic amounts of CuI were used, even at a reaction temperature as low as 60 °C, with optimal yields being obtained

### Table 1: Optimization studies for the intramolecular direct arylation of triazole 3a.

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>ligand</th>
<th>T [°C]</th>
<th>isolated yield [%]</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>LiOtoday-Bu</td>
<td>–</td>
<td>140</td>
<td>82</td>
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<tr>
<td>2</td>
<td>LiOtoday-Bu</td>
<td>–</td>
<td>120</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>LiOtoday-Bu</td>
<td>–</td>
<td>100</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>LiOtoday-Bu</td>
<td>–</td>
<td>80</td>
<td>93</td>
</tr>
<tr>
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<td>LiOtoday-Bu</td>
<td>–</td>
<td>60</td>
<td>72</td>
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<tr>
<td>6</td>
<td>LiOtoday-Bu</td>
<td>–</td>
<td>20</td>
<td>&lt;2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>K&lt;sub&gt;3&lt;/sub&gt;PO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>DMEDA</td>
<td>140</td>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>K&lt;sub&gt;3&lt;/sub&gt;PO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>N,N-dimethylglycine</td>
<td>140</td>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
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<td>K&lt;sub&gt;3&lt;/sub&gt;PO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>2,2-bipyridyl</td>
<td>140</td>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>K&lt;sub&gt;3&lt;/sub&gt;PO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1,10-phenanthroline</td>
<td>140</td>
<td>11</td>
</tr>
</tbody>
</table>

<sup>a</sup> General reaction conditions: 3a (1.00 mmol), CuI (10 mol %), ligand (10 mol %), DMF (3.0 mL).

<sup>b</sup> By <sup>1</sup>H NMR spectroscopy.
Scheme 2: Copper-catalyzed sequential catalysis with alkyne 1a.

at 80 °C (Table 1, entries 1–6). While the transformation proceeded efficiently with LiOt-Bu as the stoichiometric base, K3PO4 only led to unsatisfactory results, even when additional stabilizing ligands were used (Table 1, entries 7–10).

With optimized reaction conditions for the intramolecular direct arylation in hand, we tested the possibility of its implementation in a sequential synthesis of 1,4-dihydrochromeno[3,4-d][1,2,3]triazole (4b, Scheme 2). We were delighted to observe that the desired reaction sequence consisting of a copper-catalyzed 1,3-dipolar cycloaddition and an intramolecular C–H bond arylation converted alkyne 1a to the desired product 4b with high catalytic efficacy.

Subsequently, we explored the extension of this approach to the development of a chemoselective three-component one-pot reaction. Thus, we found that alkyl bromides 2 could be directly employed as user-friendly substrates for the in situ formation of the corresponding organic azides (Scheme 3). Notably, the catalytic system proved broadly applicable, and a variety of organic electrophiles 2, thereby, delivered differently decorated N-substituted 1,4-dihydrochromeno[3,4-d][1,2,3]triazoles 4.

Importantly, performing the one-pot reaction in a sequential fashion was not found to be mandatory. Indeed, our strategy turned out to be viable in a nonsequential manner by directly employing equimolar amounts of the three substrates. Hence,
inexpensive Cul allowed the direct assembly of aryl iodides 1, alkyl bromides 2 and NaN₃ with excellent chemose- and regioselectivities (Scheme 4). Thereby, a variety of annulated 1,2,3-triazoles 4 were obtained, featuring six- or seven-membered rings as key structural motifs. It is particularly noteworthy that the copper-catalyzed transformation enabled the formation of one C–C and three C–N bonds in a chemoselective manner, and thereby provided atom- and step-economical access to annulated carbo- as well as O- and N-heterocycles.

Finally, we found that the catalytic system also proved to be applicable to the one-pot copper-catalyzed direct arylation of various azoles 5 through N–H/C–H bond cleavages with aryl iodides 6 as the organic electrophiles (Scheme 5).

**Conclusion**

In summary, we have reported on the use of inexpensive copper(I) complexes for step- and atom-economical sequential catalytic transformations involving direct C–H bond arylations. Thus, Cul enabled the synthesis of fully substituted 1,2,3-triazoles through cascade reactions consisting of copper(I)-catalyzed [3 + 2]-azide–alkyne cycloadditions (CuAAC) and intramolecular C–H bond arylations. Notably, the optimized copper catalyst accelerated two mechanistically distinct transformations, which set the stage for the formation of up to one C–C and three C–N bonds in a chemo- and regioselective fashion, and also allowed for twofold C–H/N–H bond arylations on various azoles.

**Experimental**

**General information**

Catalytic reactions were carried out under an inert atmosphere of nitrogen using predried glassware. All chemicals were used as received without further purification unless otherwise specified. DMF was dried over CaH₂. Alkynes 1 [89-92] and triazoles 3 [93] were synthesized according to previously described methods. Cul (99.999%) was purchased from ABCR with the following specifications: Ag <3 ppm, Ca = 2 ppm, Fe = 1 ppm, Mg <1 ppm, Zn <1 ppm. Yields refer to isolated compounds, estimated to be >95 % pure, as determined by ¹H NMR. Thin-
Scheme 5: Copper-catalyzed one-pot twofold C–H/N–H arylation with azoles 5. *Reaction performed at 120 °C.

Supporting Information

Supporting Information containing all experimental details and analytical data of new compounds as well as their $^1$H and $^{13}$C spectra are provided.

Supporting Information File 1

Experimental procedures, characterization data, and NMR spectra for new compounds. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-202-S1.pdf]

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References


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