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Copper-mediated C-H(sp^2)/C-H(sp^3) coupling of benzoic acid derivatives with ethyl cyanoacetate: an expedient route to isoquinolinone scaffold †

Wei Zhu, Dengyou Zhang, Nan Yang, Hong Liu*

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A facile, copper-mediated, direct C-H(sp^2)/C-H(sp^3) bond coupling of benzoic acid derivatives with ethyl cyanoacetate by the deployment of an 8-aminoquinoline moiety as a bidentate directing group is disclosed. Such a unique transformation provides a new strategy for the construction of isoquinolinone scaffold as one of privileged cores.

In the past decade, the metal-mediated functionalization of carbon-hydrogen bonds has emerged as a powerful and promising method for the formation of carbon-carbon and carbon-heteroatom bonds in a single synthetic operation.1 In general, a wide range of noble metals including Pd,2 Au,3 Rh,4 and Ru,5 are highly active catalysts for C-H functionalization. From the point of practicality and applicability in academic and industrial communities, however, huge challenges still remain in the development of economical and efficient transformation systems for the inert C-H bond.

Among the various deployed metals, copper has attracted increasing attention because it is low-cost, environmentally-benign and abundant.6 More recently, combinations of copper salts with bidentate directing groups, involving N, N′-dual coordinated sites, have emerged as an innovative strategy for the construction of carbon-heteroatom or carbon-carbon bonds through C-H cleavage.7 Daugulis and Stahl successfully demonstrated that aren C-H bonds could be transformed into C-X bonds (X = S, O, N, F) with 8-aminoquinolines as directing groups.8 By the employment of the similar approach, Miura disclosed an efficient copper-mediated C-H/C-H coupling of benzoic acid derivatives with 1,3-azoles bearing active sp^2 C-H groups (Scheme 1).9

Despite this significant progress, to our knowledge, copper-mediated C-H(sp^2)/C-H(sp^3) coupling remains a great challenge for synthetic chemists. Previous studies have demonstrated the copper-mediated coupling of prefunctionalized aromatic derivatives with substrates bearing active methylenes10 such as malonate,11 3-oxobutanoate11a,12 and 2-cyanoacetate13 to the formation of C-C bonds. In light of these works, we desired to test such transformations via C-H cleavage, which might be facilitated by the employment of copper salts with bidentate directing groups. Herein, we revealed the copper-mediated, direct C-C bond construction of ortho C-H bond in an aromatic amide with ethyl cyanoacetate, along with simultaneous C-N bond formation. Such a unique transformation allows for the smooth construction of isoquinolinone scaffold, which stands for one of privileged moieties, which were ubiquitous in natural products and pharmaceuticals.14

We initiated our investigations by screening the reported bidentate directing groups (A, B, C, D) as they play a significant role in metal coordination (Table 1, entries 1-4). After extensive attempts, it was interesting to find that the 8-aminoquinoline-containing secondary amide (A) combined with copper salts enabled the direct C-H(sp^2)/C-H(sp^3) coupling with ethyl cyanoacetate, along with the sequential formation of the C-N bond, resulting in the construction of the isoquinolinone scaffold (entry 1). However, no reaction occurred when 8-aminoquinoline (A) was replaced with naphthalene (entry 5), indicating that coordination in an N, N′ fashion is a key step in the reaction. Other substrates with active methylenes, such as malonate, 2-phenylacetanilide, were also explored without the corresponding products observed. Further optimization of reaction conditions with respect to copper (II) salts, bases and solvents was summarized in Table 1. Using K₂CO₃ as the base and DMSO as the solvent at 110 °C, we found that the counter ions of copper(II) salts superior to the other alkali carbonates (entry 1 and entries 9-11). The yield was further improved by lowering the temperature from Miura’s work.

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Scheme 1. Copper-mediated C-H/C-H coupling with with 8-aminoquinolines as directing groups.
110°C to 90°C and reducing the reaction time to 4 h (entry 11). The effects of various solvents on the reaction were investigated. The use of aprotic solvent iPrOH (entry 13) and nonpolar solvent DCE (entry 14) was ineffective, while DMF (entry 15) was apparently inferior to DMSO. The yield was slightly decreased with the presence of TEMPO (entry 16).

With the optimized conditions identified, we next explored a series of 8-aminoquinoline benzamides to examine the scope and limitations of this process. As shown in Table 2, the desired products 3b-3r were obtained in moderate to good yields (49%-86%) by the treatment of various benzamides (1b-1r) with ethyl cyanoacetate 2a. The introduction of electron-donating groups (Me, -OMe) at the para-position of the benzamides resulted in a slight reduction in yields of target compounds (3b, 3c), while substrates bearing electron-withdrawing substituents (-CF3, -COOMe) afforded higher yields (3d, 3e). Notably, the halides such as fluoride (3f), chloride (3g, 3i) and bromide (3h) were tolerated under the standard reaction conditions, guaranteeing further transformation. The cleavage of C-H bonds in meta-substituted benzamides occurred predominantly at sterically less congested sites, irrespective of the electronic nature of the substituents (3i-3l). Ortho-substituted benzamides were also compatible, and gave good yields (3m, 3n). Naphthalene derivatives worked well, and the C-H functionalization of 2- naphthamide occurred predominantly at the less sterically-hindered β-site (3o, 3p). Benzamides bearing substituted naphthamide rings also afforded good yields.

Next, we investigated a variety of cyano-substrates as coupling partners (Table 3). Variation of the ester group had little effect on this transformation; isoquinolinone products were obtained in good yields (3q-3u), while the benzyl derivative gave moderate yield (3v). Apart from cyano substituted esters, we also tested cyano substituted amide, phosphonate and methylsulfonyl. Gratifyingly, the corresponding isoquinolinone products were obtained in good yields (3w-3y).

Table 1. Optimization of the reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>DG</th>
<th>Copper salts</th>
<th>Bases</th>
<th>Solvents</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
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<td>1</td>
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<td>Cu(OAc)2</td>
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<td>DMSO</td>
<td>N.R.</td>
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<td>K2CO3</td>
<td>DMSO</td>
<td>N.R.</td>
</tr>
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<td>K2CO3</td>
<td>DMSO</td>
<td>N.R.</td>
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<tr>
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</tr>
<tr>
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<td>Na2CO3</td>
<td>DMSO</td>
<td>88</td>
</tr>
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<td>Cu(OAc)2</td>
<td>Na2CO3</td>
<td>iPrOH</td>
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<tr>
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<tr>
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<td>Cu(OAc)2</td>
<td>Na2CO3</td>
<td>DMSO</td>
<td>74</td>
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</table>

* Reaction conditions: 1 (0.4 mmol), Ethyl cyanoacetate (1.2 mmol), copper salts (1.2 mmol), 110 °C, 12 h, Ar. * Isolated yield. * 4 h, 90 °C. * 0.4 mmol TEMPO (1eq) was added.

To get some insights into the mechanism of this cascade reaction, a series of controlled experiments were conducted. A stoichiometric amount of TEMPO, frequently used as radical scavenger in transition-metal-mediated reactions, had a slight effect on this transformation, indicating a free-radical pathway might be excluded (Table 1, entry 16). 2-(cyanomethyl)benzamide 4 could be smoothly transformed to the target molecule 3a with high yield, while ortho-blocked benzamide 1m failed to generate neither the imino product 6 nor the enamine 7 under standard condition with 96% recovery of 1m, which demonstrated that this tandem reaction first underwent the direct oxidative C(sp2)–H/C(sp3)–H cross-coupling followed by the intramolecular annulation to form the isoquinolinone scaffold (Scheme S1 in the ESI).

Table 2. Copper-mediated reaction of ethyl cyanoacetate with carboxylic acid derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>DG</th>
<th>Copper salts</th>
<th>Bases</th>
<th>Solvents</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>A</td>
<td>Cu(OAc)2</td>
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<td>B</td>
<td>Cu(OAc)2</td>
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<td>DMSO</td>
<td>N.R.</td>
</tr>
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<td>C</td>
<td>Cu(OAc)2</td>
<td>K2CO3</td>
<td>DMSO</td>
<td>N.R.</td>
</tr>
<tr>
<td>4</td>
<td>D</td>
<td>Cu(OAc)2</td>
<td>K2CO3</td>
<td>DMSO</td>
<td>N.R.</td>
</tr>
<tr>
<td>5</td>
<td>E</td>
<td>Cu(OAc)2</td>
<td>K2CO3</td>
<td>DMSO</td>
<td>N.R.</td>
</tr>
<tr>
<td>6</td>
<td>A</td>
<td>Cu(OAc)2H2O</td>
<td>K2CO3</td>
<td>DMSO</td>
<td>77</td>
</tr>
<tr>
<td>7</td>
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</tr>
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<td>A</td>
<td>Cu2</td>
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<tr>
<td>9</td>
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<td>Cu(OAc)2</td>
<td>Na2CO3</td>
<td>DMSO</td>
<td>74</td>
</tr>
</tbody>
</table>

* Reaction conditions: 1 (0.4 mmol), Ethyl cyanoacetate (1.2 mmol), copper salts (1.2 mmol), 90 °C, 12 h, Ar. * Isolated yield. * α-isomer yield: 11%
Table 3. Copper-mediated reaction of N-(quinolin-8-yl)benzamide with

cyano-substrates* 

| Reaction conditions: | 1 (0.4 mmol), M2 (1.2 mmol), copper salts (1.2 mmol), 90 °C, 4-6 h, Ar. |

Note: *The reaction temperature was 90 °C.

Scheme 2. Plausible reaction mechanism

In conclusion, we have developed a copper-mediated C-H / C-H coupling of benzoic acid derivatives and ethyl cyanoacetate, along with simultaneous C=N bond formation, under the aid of 8-aminoquinoline-based double N,N'-coordination strategy. The transformation exhibits wide generality, functional tolerance and high stereoselectivity. It also provide a straightforward means for the construction of isoquinolinone scaffold, which is a privilege moiety and ubiquitous in natural products and pharmaceuticals. Further elucidation of the detailed mechanism and application of this transformation are under investigation in our laboratory.

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Notes and references


