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Pyridine-enabled copper-promoted cross dehydrogenative coupling of C(sp²)–H and unactivated C(sp³)–H bonds†

Xuesong Wu, Yan Zhao and Haibo Ge*

The pyridine-enabled cross dehydrogenative coupling of sp² C–H bonds of polyfluoroarenes and unactivated sp³ C–H bonds of amides was achieved via a copper-promoted process with good functional group compatibility. This reaction showed great site-selectivity by favoring the sp² C–H bonds ortho to two fluoro atoms of arenes and the sp³ C–H bonds of α-methyl groups over those of the α-methylene, β- or γ-methyl groups of the aliphatic amides. Mechanistic studies revealed that sp³ C–H bond cleavage is an irreversible but not the rate-determining step, and the sp² C–H functionalization of arenes appears precedent to the sp³ C–H functionalization of amides in this process.

**Introduction**

Transition metal-promoted direct functionalization of unactivated C–H bonds is a highly valuable approach for the selective construction of C–C bonds, and considerable efforts have been devoted into this research area over the past couple of decades. Within this reaction category, ligand-assisted cross dehydrogenative coupling (CDC) is of current interest, and significant progress has been achieved in recent years. Compared with the conventional cross coupling reactions, this method enables the direct manipulation of aromatic and aliphatic C–H bonds by obviating the pre-installation of the functional groups. Moreover, the ligand acts as a directing group to ensure the high site-selectivity. In the process, a noble metal species such as palladium, rhodium, or ruthenium is often employed as a catalyst.

**Results and discussion**

Our investigation commenced with cross dehydrogenative coupling of 2-ethyl-2-methyl-N-(quinolin-8-yl)pentanamide (1a) and pentafluorobenzene (2a) in 1,4-dioxane with stoichiometric amounts of Cu(OAc)₂ under atmospheric oxygen (Scheme 1a). After an extensive screening of the bases, pyridine has proven to be optimal, affording the desired product 3a in 22% yield, while all inorganic bases failed in the reaction (entries 1–7).

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† Electronic supplementary information (ESI) available: Experimental details including characterization data, copies of 1H, 13C NMR and NOESY spectra. See DOI: 10.1039/c5sc02143j
that pyridine could also act as a ligand in the process, and thus promote the reaction, a screening of nitrogen-containing potential bidentate ligands was further carried out. As shown in Table 1, several ligands such as TMEDA, 2,2'-bipyridine, and 1,10-phenanthroline could promote the process, but none of these molecules is as effective as pyridine (entries 8–10). Next, different copper sources were examined, and it was found that CuOAc was the only other species, but with less efficiency (entry 13). Then, the effects of an oxidant towards the reaction were examined, and it turned out that di-tert-butyl peroxide was optimal, providing 3a in 44% yield (entry 17). It was also noted that a higher yield could be obtained under atmospheric nitrogen (entry 18). Following the above investigation, we carried out an extensive screening of the solvents, and the reaction was significantly improved with the solvent mixture of DME and 1,4-dioxane (entry 22). Furthermore, an excellent yield was observed with increased amounts of pyridine (entry 24). It was also noted that the reaction yield was dramatically decreased with reduced amounts of the copper species (entry 25), presumably due to the competitive coordination of pyridine or tert-butanolate released from di-tert-butyl peroxide to copper.

Moreover, it is clear that pyridine is required for this process since no apparent product formation occurred in the absence of pyridine (entry 26). As expected, a high site-selectivity was observed with a preference for the C–H bond of the a-position over that of the a-methylene, b- or y-methyl group, which is believed to arise from the steric effect and preference for the formation of a five-membered ring intermediate over the six- or seven-membered ring intermediate in the cyclometalation step.

Under the optimized conditions, the scope with respect to fluoroarenes was examined. As shown in Table 2, tetrafluorobenzenes bearing a methoxy, bromo, cyano, or trifluoromethyl group were compatible with the process (3b–e). Additionally, higher yields were observed with substrates substituted by an electron-withdrawing group, presumably due to the increased reactivity of the aromatic C–H bonds from the increased acidity of these bonds and/or increased electronegativity of a copper intermediate which facilitates the sp3 C–H bond activation. Furthermore, 1,2,3,5-tetrafluorobenzene, 1,2,4,5-tetrafluorobenzene, and trifluorobenzenes with an additional electron-withdrawing group were effective substrates (3f–i). Not surprisingly, low reactivity was observed with 1,3,5-

### Table 1: Optimization of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu salt</th>
<th>Oxidant</th>
<th>Additive (eq.)</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OAc)₂</td>
<td>K₂CO₃</td>
<td>(2)</td>
<td>1,4-Dioxane</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)₂</td>
<td>K₂HPO₄</td>
<td>(2)</td>
<td>1,4-Dioxane</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)₂</td>
<td>PhCO₂Na</td>
<td>(2)</td>
<td>1,4-Dioxane</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)₂</td>
<td>H₂SO₄</td>
<td>(2)</td>
<td>1,4-Dioxane</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)₂</td>
<td>Py (2)</td>
<td></td>
<td>1,4-Dioxane</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>Cu(OAc)₂</td>
<td>2,6-Lutidine (2)</td>
<td>1,4-Dioxane</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Cu(OAc)₂</td>
<td>DMAP (2)</td>
<td></td>
<td>1,4-Dioxane</td>
<td>17</td>
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<tr>
<td>8</td>
<td>Cu(OAc)₂</td>
<td>TMEDA (1)</td>
<td></td>
<td>1,4-Dioxane</td>
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<tr>
<td>9</td>
<td>Cu(OAc)₂</td>
<td>2,2'-Dipyridyl (1)</td>
<td>1,4-Dioxane</td>
<td>16</td>
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<tr>
<td>10</td>
<td>Cu(OAc)₂</td>
<td>1,10-Phen (1)</td>
<td></td>
<td>&lt;5</td>
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<tr>
<td>11</td>
<td>CuCl₂</td>
<td>Py (2)</td>
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<td>1,4-Dioxane</td>
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<tr>
<td>12</td>
<td>CuBr₂</td>
<td>Py (2)</td>
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<tr>
<td>13</td>
<td>CuOAc</td>
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<tr>
<td>14</td>
<td>CuBr</td>
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<td>1,4-Dioxane</td>
<td>0</td>
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<tr>
<td>15</td>
<td>Cu(OAc)₂</td>
<td>Ag₂O</td>
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<tr>
<td>16</td>
<td>Cu(OAc)₂</td>
<td>TBHP</td>
<td>Py (2)</td>
<td>1,4-Dioxane</td>
<td>10</td>
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<tr>
<td>17</td>
<td>Cu(OAc)₂</td>
<td>(t-BuO₂)₃</td>
<td>Py (2)</td>
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<tr>
<td>18f</td>
<td>Cu(OAc)₂</td>
<td>(t-BuO₂)₃</td>
<td>Py (2)</td>
<td>1,4-Dioxane</td>
<td>59</td>
</tr>
<tr>
<td>19f</td>
<td>Cu(OAc)₂</td>
<td>(t-BuO₂)₃</td>
<td>Py (2)</td>
<td>DME</td>
<td>46</td>
</tr>
<tr>
<td>20f</td>
<td>Cu(OAc)₂</td>
<td>(t-BuO₂)₃</td>
<td>Py (2)</td>
<td>THF</td>
<td>40</td>
</tr>
<tr>
<td>21f</td>
<td>Cu(OAc)₂</td>
<td>(t-BuO₂)₃</td>
<td>Py (2)</td>
<td>Toluene</td>
<td>15</td>
</tr>
<tr>
<td>22f</td>
<td>Cu(OAc)₂</td>
<td>(t-BuO₂)₃</td>
<td>Py (2)</td>
<td>DME,1,4-dioxane (7 : 3)</td>
<td>84</td>
</tr>
<tr>
<td>23f</td>
<td>Cu(OAc)₂</td>
<td>(t-BuO₂)₃</td>
<td>Py (1)</td>
<td>DME,1,4-dioxane (7 : 3)</td>
<td>50</td>
</tr>
<tr>
<td>24f</td>
<td>Cu(OAc)₂</td>
<td>(t-BuO₂)₃</td>
<td>Py (3)</td>
<td>DME,1,4-dioxane (7 : 3)</td>
<td>96 [92]</td>
</tr>
<tr>
<td>25f</td>
<td>Cu(OAc)₂</td>
<td>(t-BuO₂)₃</td>
<td>Py (3)</td>
<td>DME,1,4-dioxane (7 : 3)</td>
<td>63</td>
</tr>
<tr>
<td>26f</td>
<td>Cu(OAc)₂</td>
<td>(t-BuO₂)₃</td>
<td>—</td>
<td>DME,1,4-dioxane (7 : 3)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Reaction conditions: 1a (0.3 mmol), 2a (0.6 mmol), Cu salt (0.3 mmol), oxidant (0.75 mmol), additive, 1.0 mL of solvent, 140 °C, 16 h. Yields and conversions are based on 1a, determined by 1H-NMR using dibromomethane as the internal standard. Isolated yield is in parenthesis. Under N₂ atmosphere. Cu(OAc)₂ (0.15 mmol), Q = 8-quinolinyl.
Notably, both mono- and di-pentafluoro-substituted coupling products were obtained with 2,2-dimethyl butanamide and trifluoropropanamide (3w and 3x). Interestingly, only the mono-coupling products were observed with α-phthalimide and α-sulfone-substituted amides, which is believed to be due to the steric effects (3y and 3z). Not surprisingly, both mono- and bis-coupling products were isolated with N-(quinolin-8-yl)pivalamide (3aa). Moreover, it was found that a tertiary α-carbon is necessary for this reaction since amides 4 and 5 failed to provide the corresponding desired products. Unfortunately, functionalization of secondary β-sp³ carbons was not successful (6 and 7).

To gain some mechanistic insights into this reaction, a series of deuterium-labeling experiments were carried out (Scheme 2). Considering that ‘BuOH is generated from (‘BuO)₂ as a byproduct in the process, stoichiometric amounts of ‘BuOD was added to the reaction system for this study. It was noted that an apparent H/D exchange occurred with pentafluorobenzene (2a) with or without 2-ethyl-2-methyl-N-(quinolin-8-yl)butanamide (1b), indicating that C–H bond cleavage of fluorobenzene is a reversible step. Furthermore, either a small or trace amount of [D]-2a was observed in the absence of Cu(OAc)₂ or pyridine, while the obvious H–D scrambling occurred without (‘BuO)₂. It should be mentioned that H–D scrambling could also be promoted by CuOAc instead of Cu(OAc)₂ in the absence of (‘BuO)₂. These results suggest that the copper species promotes the sp³ C–H bond cleavage with the pyridine as a base and ligand to facilitate the process, and a pyridine-coordinated aryl copperII or aryl copperI intermediate may be involved in the reaction. In the study, it was found that H/D exchange did not happen with 1b in the absence of 2a, indicating that an aryl copper intermediate may be involved in the sp³ C–H bond cleavage step of the amide.

We further carried out deuterium-labeling experiments with [D]-1b. As shown in Scheme 3, a H/D exchange was not observed with either this substrate or the product, suggesting that sp³ C–H bond cleavage is an irreversible step. In addition, a second order kinetic isotope effect was observed with 1b in the process, indicating that cyclometalation of the amide is not the rate-limiting step.

On the basis of the above observed results and the previous reports, a plausible mechanism for this reaction is proposed (Scheme 4). It is believed that this process begins with the reversible C–H cupration of a fluoro(hetero)arene with Cu(OAc)₂ in the presence of pyridine. Coordination of amide 1 to this CuⅡ species followed by a ligand exchange step gives rise to the CuⅢ intermediate B. Subsequent oxidation of the CuⅢ species B generates the CuⅣ intermediate C, which undergoes an intramolecular cyclometalation step to provide the CuⅤ complex D. Reductive elimination of this intermediate followed by a ligand dissociation process affords the product 3 and a CuⅠ species. Oxidation of the CuⅠ species by (‘BuO)₂ regenerates the CuⅡ species. Alternatively, on the basis of the observations in Scheme 2, the cupration of fluoro(hetero)arene 2 could take place with the CuⅠ species, providing the CuⅡ intermediate F which could then be oxidized to the CuⅢ intermediate A by (‘BuO)₂.

### Table 2 Scope of fluoroarenes

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Reaction conditions:</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et-O-Q</td>
<td>1a (0.3 mmol), 2 (0.6 mmol), Cu(OAc)₂ (0.3 mmol), (‘BuO)₂ (0.75 mmol), Py (0.9 mmol), DME/1,4-dioxane (v/v = 7 : 3, 1.0 mL), 140 °C, 16 h.</td>
<td>92%</td>
</tr>
<tr>
<td>F</td>
<td>3a, 92% F; 3b, 71% F; 3e, 80% F; 3d, 85% F; 3f, 94% F; 3g, 84% F; 3h, 73% F; 3i, 92% F; 3j, 81% F; 3k, 80% F; 3l, 77% F; 3m, 79% F; 3n, 83% F</td>
<td></td>
</tr>
</tbody>
</table>

Footnotes:

* Reaction conditions: 1a (0.3 mmol), 2 (0.6 mmol), Cu(OAc)₂ (0.3 mmol), (‘BuO)₂ (0.75 mmol), Py (0.9 mmol), DME/1,4-dioxane (v/v = 7 : 3, 1.0 mL), 140 °C, 16 h. Isolated yield.

#### Next...

The substrate scope study of aliphatic amides was achieved at an elevated reaction temperature (3j–l). Interestingly, a high regioselectivity was also observed in these cases by favoring the C(α)-alkylated products. Delightfully, successful couplings of these substrates were achieved at an elevated reaction temperature (3m and 3n). Unfortunately, other heteroaromatic substrates such as benzoxazoles, thiophenes, indoles etc. failed to provide any desired products under the current conditions.

The substrate scope study of aliphatic amides was investigated (Table 3). As expected, 2,2-disubstituted propionamides bearing either the linear or cyclic chains provided the corresponding desired products in good yields with good functional group compatibility. In addition, a predominant preference for functionalizing the C–H bonds of the α-methyl over those of the α-methylene, β- or γ-methyl groups, was observed in all cases, presumably due to the steric effect.
Conclusions

In summary, copper-promoted pyridine-enabled cross dehydrogenative coupling of aromatic sp² C–H bonds and unactivated aliphatic sp³ C–H bonds was developed with high efficiency and good functional group tolerance. In this process, high regioselectivity was observed with sp² C–H bond functionalization, favoring an sp² C–H bond between two C–F bonds of (hetero)arenes. In addition, a predominant preference for functionalizing the sp³ C–H bonds of α-methyl groups over those of the α-methylene, β- or γ-methyl groups was observed with aliphatic amides. Mechanistic studies suggested that sp² C–H bond cleavage is a reversible step while sp³ C–H bond cleavage is an irreversible but not the rate-limiting step. Interestingly, it was also found that sp³ C–H bond cleavage is a reversible step while sp³ C–H bond cleavage is an irreversible but not the rate-limiting step. The detailed mechanistic studies and potential synthetic applications of this process are currently under investigation in our laboratory.

Acknowledgements

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Notes and references


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