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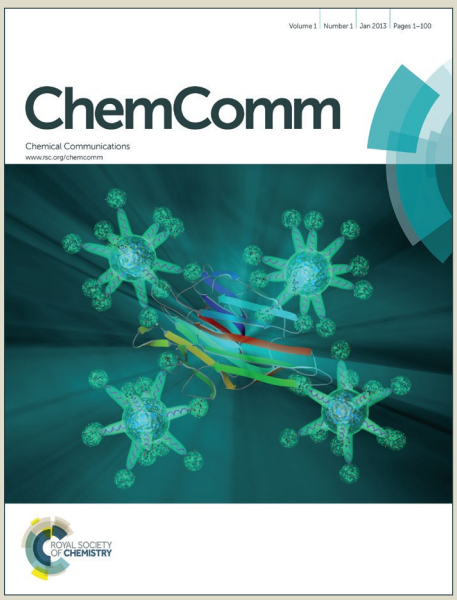





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# Copper Mediated Decarboxylative Direct C–H Arylation of Heteroarenes with Benzoic Acids†

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**Decarboxylative coupling reactions till date required stoichiometric oxidant (such as copper and silver salts) for decarboxylation purpose along with a metal catalyst (e.g. palladium) for cross coupling. In this communication, an economic and sustainable approach by using simple copper salt was developed in presence of molecular oxygen as the sole-oxidant. A wide range of 5-membered heteroarenes undergo aryl-heteroaryl cross-coupling with electron deficient aryl carboxylic acids.**

Five membered heterocycles are recognized as important structural motifs in pharmaceuticals, agrochemicals, natural products, functional organic materials and dye industries (Figure 1).[1] In this context, synthetic importance of azole derivatives ensured continuous interest of chemists to find effective methods for regiospecific formation of aryl-heteroaryl bond.[2]

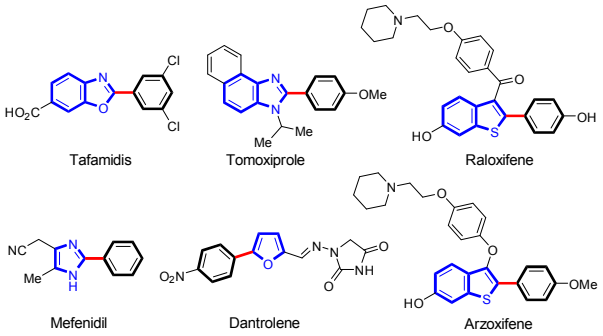
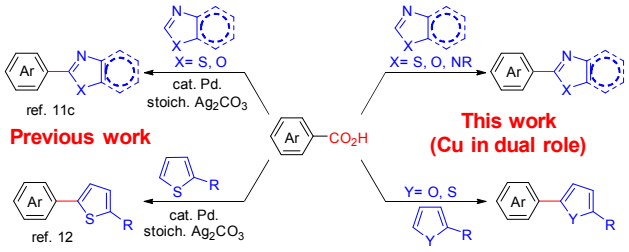



**Figure 1.** Few relevant aryl-heterocyclic cores in drug molecules

Traditional cross-coupling methods generally require expensive heavy transition metals, pre-activated organometallic coupling partners and as a result, these methods often produce toxic and stoichiometric side-products.[3] Alternatively, carboxylic acids are an exciting choice in place of traditional organometallic counterpart since they are widely available, inexpensive and easy to store and handle.[4] Most importantly, transition metal catalyzed decarboxylation of aromatic carboxylic acids can provide same aryl-metal intermediates by loss of $CO_2$.[5]

Over recent years, benzoic acid derivatives have been popularized mainly by Goossen[6] and others[7] as an alternative coupling partner with aryl halides and triflates.[8] Consequently, direct C–H arylation reactions have been a prominent field of research since such transformations are capable of streamlining organic synthesis and minimizing wasteful byproducts.[9] Therefore, a decarboxylative C–H bond functionalization that combines these two newly emerging approaches, that is, decarboxylation and direct C–H bond functionalization, holds a great potential for new bond forming strategies in synthesis. Interestingly, few methods have already been reported using this decarboxylative direct arylation approach. In these cases either Cu or Ag salt is used in stoichiometric amount for decarboxylation purpose.[10] Additionally, a Pd catalyst was often employed for cross coupling.[11,12] Employment of an economic, greener first row transition metal, for example copper, to play the dual role of decarboxylation followed by direct C–H arylation in presence of molecular oxygen is yet to be explored (Scheme 1).




**Scheme 1.** Decarboxylative C–H arylation of heteroarenes

Copper mediated methods for protodecarboxylation are well studied in literature.[13,14] Additionally, copper is also used

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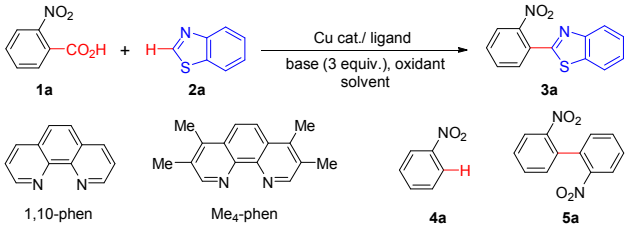
broadly in different C–H functionalization reactions.[15] Surprisingly, simple copper catalyzed/mediated method for decarboxylative direct C–H arylation is under developed albeit of its practical importance and high demand in present context. Herein we report first copper mediated C–H arylation of benzoic acid derivatives with different heteroarenes (Scheme 1) using molecular $O_2$.

**Table 1.** Optimization of reaction condition[16,a]

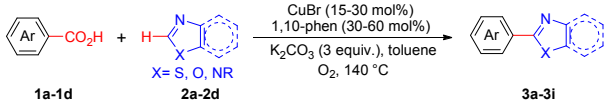



| Entry | [Cu] | ligand | base | [O] | **3a** (%) |
|---|---|---|---|---|---|
| 1 | $CuCl_2$ | 1,10-phen | $K_2CO_3$ | air | 16 |
| 2 | $CuBr_2$ | 1,10-phen | $K_2CO_3$ | air | 20 |
| 3 | CuBr | 1,10-phen | $K_2CO_3$ | air | 27 |
| 4 | CuBr | bipy | $K_2CO_3$ | air | 16 |
| 5 | CuBr | TMEDA | $K_2CO_3$ | air | 14 |
| 6 | CuBr | $Me_4$-phen | $K_2CO_3$ | air | 25 |
| 7 | CuBr | -- | $K_2CO_3$ | air | <1 |
| 8 | CuBr | 1,10-phen | $KHCO_3$ | air | 12 |
| 9 | CuBr | 1,10-phen | KF | air | 24 |
| 10 | CuBr | 1,10-phen | $K_2CO_3$ | $K_2S_2O_8$ | 20 |
| 11 | CuBr | 1,10-phen | $K_2CO_3$ | DTBP | 28 |
| 12 | CuBr | 1,10-phen | $K_2CO_3$ | $O_2$ | 57 |
| 13[b] | CuBr | 1,10-phen | $K_2CO_3$ | $O_2$ | 63 |
| 14[b,c] | CuBr | 1,10-phen | $K_2CO_3$ | $O_2$ | 71 |
| 15 | -- | 1,10-phen | $K_2CO_3$ | $O_2$ | - |
| **16**[b,c,d] | **CuBr** | **1,10-phen** | **$K_2CO_3$** | **$O_2$** | **76** |
| 17[e] | CuBr | 1,10-phen | $K_2CO_3$ | $O_2$ | 53 |

[a]Reaction conditions: **1** (0.6 mmol), Cu salt (30 mol%), ligand (60 mol%), base (3 equiv.), **2** (0.2 mmol) in toluene (1 mL) at 130 °C for 24 h. Yields were determined by gas chromatography using *n*-decane as internal standard. [b]25 mol% DTBP was used. [c]4 Å MS (30 mg). [d]140 °C. [e]Cu salt (15 mol%), ligand (30 mol%).

At the outset, we hypothesized that benzoic acid derivatives in presence of suitable copper salt can effectively produce direct C–H arylation product with 5-membered heteroarenes in regioselective manner due to the intrinsic electronic bias among different C–H bonds. To test this presumption, 2-nitrobenzoic acid was employed with benzothiazole in presence of $CuCl_2$/ 1,10-phen and a base in different solvents. During optimization studies, we realized that choice of solvent plays a critical role to obtain the desired product. Polar aprotic solvent (DMSO, DMF) gave expected compound in trace amount along with undesired 2,2'-dinitro-1,1'-biphenyl (**5a**) as the major product. On the other hand, polar protic solvents (EtOH, *t*-BuOH) resulted in protodecarboxylative product, nitrobenzene (**4a**).

**Table 2.** Scope of substrates for heteroarenes with two heteroatoms[16,a]




| entry | benzoic acid | heteroarene | product | yield (%) |
|---|---|---|---|---|
| 1 | **1a** | **2a** | **3a** | 76<br>53[b] |
| 2 | **1a** | **2b** | **3b** | 71<br>51[c] |
| 3 | **1a** | **2c** | **3c** | 74<br>43[b]<br>56[c] |
| 4 | **1a** | **2d** | **3d** | 60<br>47[c] |
| 5 | **1b** | **2b** | **3e** | 78<br>49[b] |
| 6 | **1c** | **2a** | **3f** | 32 |
| 7 | **1d** | **2a** | **3g** | 36<br>23[c] |
| 8 | **1d** | **2b** | **3h** | 29 |

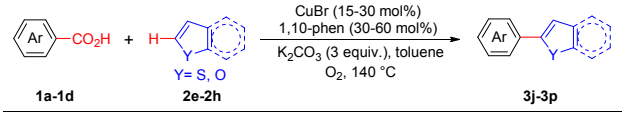
[a]Reaction conditions: **1** (0.6 mmol), CuBr (30 mol%), 1,10-phenanthrolene (60 mol%), $K_2CO_3$ (0.6 mmol), 4 Å MS (30 mg), **2** (0.2 mmol), DTBP (25 mol%) in toluene (1 mL) under $O_2$ atmosphere at 140 °C for 24 h. [b]CuBr (15 mol%), 1,10-phenanthrolene (30 mol%). [c]CuBr (20 mol%), 1,10-phenanthrolene (40 mol%).

Less polar solvents (toluene, xylene) provided desired coupling product in 15-20% yield along with varying amount of **4a** and **5a**.[16] Detailed evaluation of model reaction system by varying different copper salts and ligands revealed that CuBr along with simple 1,10-phenanthroline can promote the desired reaction (Table 1, entries 1-6). Choice of base is also crucial since in absence of base no cross-coupled product was determined, and weak bases were found to produce better results (entries 8-9).[16] Introduction of an oxidant, especially molecular oxygen improved the yield significantly. In careful control it was found that addition of 25 mol% of di-*tert*-butylperoxide (DTBP) with oxygen atmosphere can improve the yield further to 63% (entries 10-13). Increase in temperature beyond 140 °C promoted formation of **5a** significantly by suppressing desired product formation.[16] Control experiments confirmed that copper is responsible for

decarboxylation as well as direct C–H arylation (entry 15) in presence of molecular oxygen.[16]

With this optimized condition, scope of the reaction was investigated with 2-nitrobenzoic acid by varying different 5-membered heterocycles containing 2-heteroatoms. All benzothiazole, benzoxazole and benzimidazole core was found to provide desired products in good yields (Table 2, entries **3a**, **3b** and **3c**). This observation ruled out the possibility of ring opening of benzothiazole, followed by imine formation and cyclization pathway, as observed in earlier cases to deliver only benzothiazole coupled products.[17] The *N*-protected imidazole compounds also furnished decarboxylated coupling product in synthetically useful yield (entry **3d**). Chloro substituted 2-nitrobenzoic acid found effective to deliver heteroarylated product with benzoxazole (entry **3e**). During exploration of scopes for substrates we realized this current method is highly sensitive towards choice of benzoic acid. Mainly, benzoic acids with electron withdrawing groups are prone for easy decarboxylation to provide aryl-copper intermediate[14] and likely to deliver desired direct C–H arylated product. Accordingly, different fluoro substituted electron withdrawing benzoic acids were employed to obtain fluoro substituted heteroarylated coupling products successfully albeit of low yields (entries **3f**, **3g**, **3h**). Please note that decarboxylative coupling reactions are usually very sensitive towards electronic nature of the partners involved.[11]

**Table 3.** Scope of substrates for heteroarenes with one heteroatom[16,a]

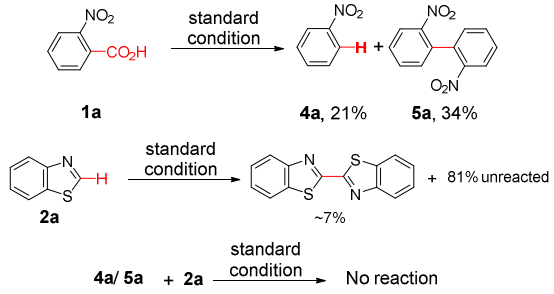



1a-1d 2e-2h 3j-3p

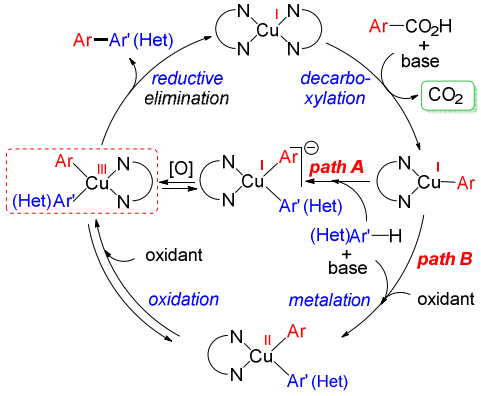
| entry | benzoic acid | heteroarene | product | yield (%) |
|---|---|---|---|---|
| 1 | **1a** | **2e** | **3i** | 83<br>54[b] |
| 2 | **1a** | **2f** | **3j** | 68<br>44[c] |
| 3 | **1a** | **2g** | **3k** | 73<br>46[c] |
| 4 | **1a** | **2h** | **3l** | 76<br>49[c] |
| 5 | **1b** | **2g** | **3m** | 70<br>57[b] |

[a]Reaction conditions: **1** (0.6 mmol), CuBr (30 mol%), 1,10-phenanthrolene (60 mol%), $K_2CO_3$ (0.6 mmol), 4 Å MS (30 mg), **2** (0.2 mmol), DTBP (25 mol%) in toluene (1 mL) under $O_2$ atmosphere at 140 °C for 24 h. [b]CuBr (15 mol%), 1,10-phenanthrolene (30 mol%). [c]CuBr (20 mol%), 1,10-phenanthrolene (40 mol%).

Next, we were intrigued by the possibility whether thiophene moiety can be employed in our current methodology or not. Thiophenes are less reactive compared to azole derivatives, and previously stoichiometric silver salts were used with palladium catalyst for decarboxylative coupling with thiophenes.[12] To our delight, benzothiophene delivered the C–H arylated product under the present reaction condition in synthetically useful yield (Table 3, entry **3i**). Next, scope of different thiophene derivatives were contemplated with 2-nitrobenzoic acid as model substrate. Aldehyde, cyano and halogen-substitutions were tolerated successfully (entries **3j**, **3k**, **3l**). We were pleased to find that not only thiophene, but furan moiety can also be used successfully in our present methods (entry **3m**). Although this newly described methodology is sensitive towards choice of benzoic acids, but enjoys a wide range of variation in heterocycles.




**Scheme 2.** Control experiments




**Scheme 3.** Plausible mechanism

After exploring scope of substrates, we tried to explicate the mechanistic complexity for this newly developed protocol. Control experiments without heterocycle provided decarboxylated products **4a** and **5a**, exclusively. Both **4a** and **5a** were unreactive during their independent reactions with heterocycle. Again, homo-coupling of benzothiazole under the reaction condition was found sluggish (Scheme 2).[16] This implies ligated copper species first forms copper salt of benzoic acid followed by extrusion of $CO_2$ to afford aryl-copper intermediate.[14] Additionally, a radical pathway may be

disfavoured as no significant drop in product yield was noticed when different radical scavengers were examined.[16] In accordance to these observations, along with recent literature reports,[18] a plausible mechanistic cycle is proposed. First, ligated copper forms aryl-copper intermediate *via* decarboxylation. Then, base assisted metalation of heteroarene with aryl-copper species may lead to either Cu(I) intermediate (pathway A) or Cu(II) intermediate (pathway B) by instantaneous oxidation. This Cu(I)/Cu(II) intermediate can undergo reversible sluggish oxidation to generate aryl-Cu(III) intermediate followed by immediate reductive elimination to provide desired direct C–H arylated product (Scheme 3). Although the exact role of oxygen is not clear, we believe it is mainly involved in formation of aryl-Cu(III) species.[19]

In summary, we have developed a useful protocol with a simple copper/1,10-phen based system in presence of molecular oxygen as the sole-oxidant for aryl-heteroaryl cross coupling employing electron deficient benzoic acids. This method is advantageous for its wide tolerance towards different heterocycles bearing one or two heteroatoms under relatively milder condition. Mechanistic understanding towards developing direct C–H arylation by copper are currently ongoing in our group.

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