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Copper mediated decarboxylative direct C–H arylation of heteroarenes with benzoic acids†

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Decarboxylative coupling reactions to date require a stoichiometric oxidant (such as copper and silver salts) for decarboxylation purposes along with a metal catalyst (*e.g.* palladium) for cross-coupling. In this communication, an economic and sustainable approach by using a simple copper salt was developed in the 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 (Fig. 1).[1] In this context, the synthetic importance of azole derivatives has ensured the continuous interest of chemists to find effective methods for regiospecific formation of aryl–heteroaryl bonds.[2]

Traditional cross-coupling methods generally require expensive heavy transition metals, and 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 counterparts 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 the 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 alternative coupling partners 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 salts are used in stoichiometric amounts for decarboxylation purposes.[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 the presence of molecular oxygen is yet to be explored (Scheme 1).

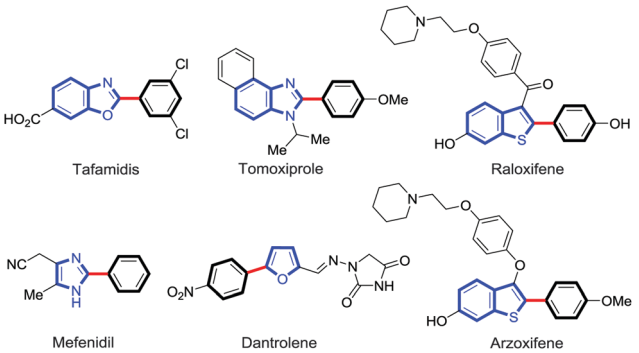
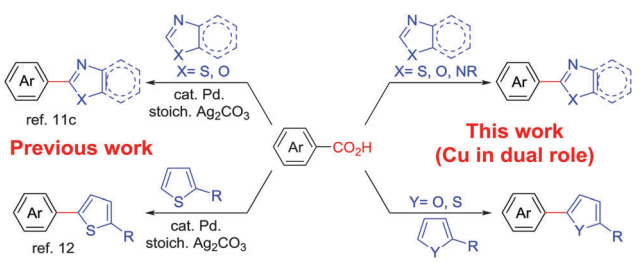


Fig. 1 Few relevant aryl-heterocyclic cores in drug molecules.

Copper mediated methods for protodecarboxylation are well studied in the literature.[13,14] Additionally, copper is also used broadly in different C–H functionalization reactions.[15]



Scheme 1 Decarboxylative C–H arylation of heteroarenes.

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† Electronic supplementary information (ESI) available: Optimization details, reaction procedure, characterization data and ^{1}H, ^{13}C NMR spectra. See DOI: 10.1039/c5cc08367b

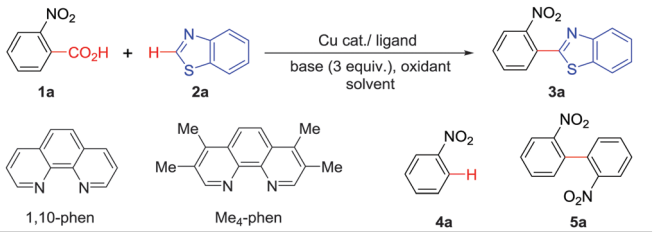
Surprisingly, a simple copper catalyzed/mediated method for decarboxylative direct C–H arylation is underdeveloped despite its practical importance and high demand in the present context. Herein we report the first copper mediated C–H arylation of benzoic acid derivatives with different heteroarenes (Scheme 1) using molecular O_2.

At the outset, we hypothesized that benzoic acid derivatives in the presence of a suitable copper salt can effectively produce direct C–H arylation products with 5-membered heteroarenes in a 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 the 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 in obtaining the desired product. Polar aprotic solvents (DMSO, DMF) gave the expected compound in trace amounts 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 a protodecarboxylative product, nitrobenzene (**4a**).

Less polar solvents (toluene, xylene) provided the desired coupling product in 15–20% yield along with varying amounts of **4a** and **5a**.[16] Detailed evaluation of the 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 the absence of base no cross-coupled product was obtained, and weak bases were found to produce better results (entries 8 and 9).[16] Introduction of an oxidant, especially molecular oxygen improved the yield significantly. Upon careful control it was found that addition of 25 mol% of di-*tert*-butylperoxide (DTBP) in an oxygen atmosphere can improve the yield further to 63% (entries 10–13). Increase in temperature beyond 140 °C promoted the 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 the presence of molecular oxygen.[16]

Under these optimized conditions, scope of the reaction was investigated with 2-nitrobenzoic acid by varying different 5-membered heterocycles containing 2-heteroatoms. All benzothiazole, benzoxazole and benzimidazole cores were

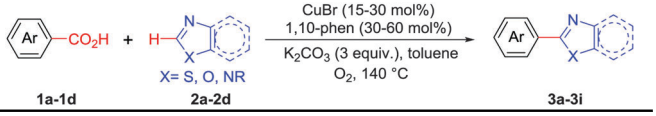
Table 1 Optimization of reaction condition[a][16]

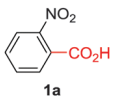
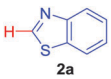
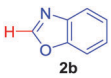
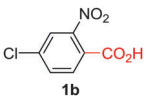
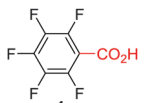
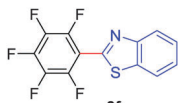
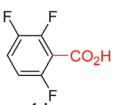
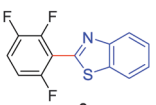
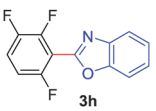


Entry	[Cu]	Ligand	Base	[O]	**3a** (%)
1	$CuCl_2$	1,10-Phen	K_2CO_3	Air	16
2	$CuBr_2$	1,10-Phen	K_2CO_3	Air	20
3	CuBr	1,10-Phen	K_2CO_3	Air	27
4	CuBr	bipy	K_2CO_3	Air	16
5	CuBr	TMEDA	K_2CO_3	Air	14
6	CuBr	Me_4-phen	K_2CO_3	Air	25
7	CuBr	—	K_2CO_3	Air	<1
8	CuBr	1,10-Phen	$KHCO_3$	Air	12
9	CuBr	1,10-Phen	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 the 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%).

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



Entry	Benzoic acid	Heteroarene	Product	Yield (%)
1				76 53[b]
2	**1a**			71 51[c]
3	**1a**			74 43[b] 56[c]
4	**1a**			60 47[c]
5		**2b**		78 49[b]
6		**2a**		32
7		**2a**		36 23[c]
8	**1a**	2b		29

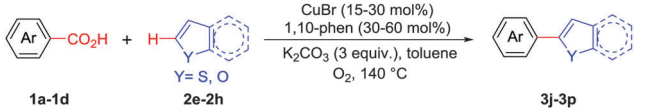
[a] Reaction conditions: **1** (0.6 mmol), CuBr (30 mol%), 1,10-phenanthrolene (60 mol%), K_2CO_3 (0.6 mmol), 4 Å MS (30 mg), **2** (0.2 mmol), DTBP (25 mol%) in toluene (1 mL) under O_2 atmosphere at 140 °C for 24 h. [b] CuBr (15 mol%), 1,10-phenanthrolene (30 mol%). [c] CuBr (20 mol%), 1,10-phenanthrolene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

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 the cyclization pathway, as observed in earlier cases to deliver only benzothiazole coupled products.[17] The *N*-protected imidazole compounds also furnished the decarboxylated coupling product in synthetically useful yield (entry **3d**). Chloro-substituted 2-nitrobenzoic acid was found to be effective to deliver the heteroarylated product with benzoxazole (entry **3e**). During exploration of scope for substrates we realized that this current method is highly sensitive to the choice of benzoic acid. Mainly, benzoic acids with electron withdrawing groups are prone to easy decarboxylation to provide an aryl–copper intermediate[14] and likely to deliver the desired direct C–H arylated product. Accordingly, different fluorosubstituted electron withdrawing benzoic acids were employed to obtain fluorosubstituted heteroarylated coupling products successfully albeit in low yields (entries **3f**, **3g**, **3h**). Please note that decarboxylative coupling reactions are usually very sensitive to the electronic nature of the partners involved.[11]

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

After exploring the scope of substrates, we tried to explicate the mechanistic complexity for this newly developed protocol. Control experiments without heterocycles provided decarboxylated products **4a** and **5a**, exclusively. Both **4a** and **5a** were unreactive during their independent reactions with heterocycles. Again, homo-coupling of benzothiazole under the reaction conditions was found to be sluggish (Scheme 2).[16] This implies that ligated copper species first forms the copper salt of benzoic acid followed by the extrusion of CO_2 to afford an 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 with these observations, along with recent literature reports,[18] a plausible mechanistic cycle is proposed. First, ligated copper forms the aryl–copper intermediate *via* decarboxylation. Then, base assisted metalation of heteroarene with aryl–copper species may lead to either the Cu(I) intermediate (pathway A) or the Cu(II) intermediate (pathway B) by instantaneous oxidation.

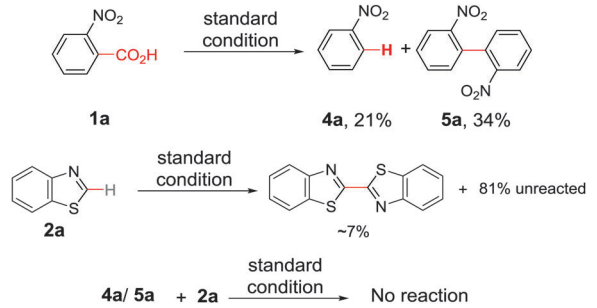
Table 3 Scope of substrates for heteroarenes with one heteroatom[a 16]



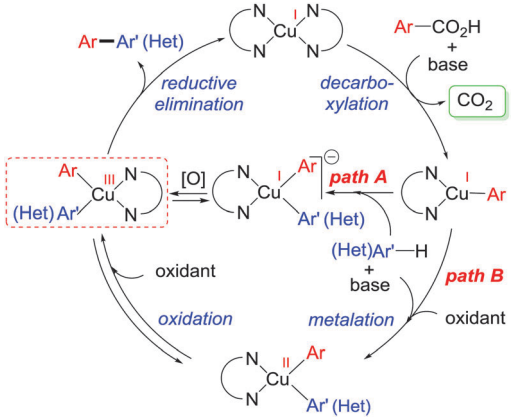
1a-1d 2e-2h 3j-3p

Entry	Benzoic acid	Heteroarene	Product	Yield (%)
1	**1a**	**2e**	**3i**	83 54[b]
2	**1a**	**2f**	**3j**	68 44[c]
3	**1a**	**2g**	**3k**	73 46[c]
4	**1a**	**2h**	**3l**	76 49[c]
5	**1b**	**2g**	**3m**	70 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%).



Scheme 2 Control experiments.



Scheme 3 Plausible mechanism.

This Cu(I)/Cu(II) intermediate can undergo reversible sluggish oxidation to generate an aryl–Cu(III) intermediate followed by immediate reductive elimination to provide the desired direct C–H arylated product (Scheme 3). Although the exact role of oxygen is not clear, we believe that it is mainly involved in the 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 the presence of molecular oxygen as the sole-oxidant for aryl–heteroaryl cross-coupling employing electron deficient benzoic acids. This method is advantageous because of its wide tolerance towards different heterocycles bearing one or two heteroatoms under relatively mild conditions. Investigation into the mechanistic understanding of the development of direct C–H arylation by copper is currently ongoing in our group.

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