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A Versatile Catalyst for Intermolecular Direct Arylation of Indoles with Benzoic Acids as Arylating Reagents

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The development of new methods for the synthesis of valuable compounds from simple and readily available starting materials through concise steps is of intense interest to the chemical community. In this context, metal-catalyzed direct functionalizations of C–H bonds are currently a very active area because these transformations have great potential to offer highly efficient synthetic routes and minimize wasteful byproducts by precluding the need for preactivation of the substrates.[1] Because of the prevalence of C2- and C3-arylindole structural units in biologically active molecules and pharmaceuticals,[2] considerable efforts have been devoted to the development of the metal-catalyzed direct arylation of indoles with various arylating reagents, leading to significant advances in this area.[3]

Recently, pioneering studies by the groups of Goossen,[4] Myers[5] and others[6] demonstrated that benzoic acids can be used as arylating reagents for the decarboxylative cross-coupling reaction, in which the organometallic intermediates generated from metal-mediated decarboxylation served as either nucleophiles or electrophiles depending on the nature of the metal ions used. The groups of Tunge[7a–d] and Schaus[7e] independently developed the palladium-catalyzed intramolecular decarboxylation of allylic esters for the formation of C–C bonds, constituting an appealing approach to complex molecules. The groups of Yu[8] and Daugulis,[9] in their elegant studies, disclosed that benzoic acids can undergo carboxylate-directed C–H functionalizations. Seminal work by Miura et al. on coupling reaction of benzoic acids with alkynes for construction of fused-rings implied that *ortho*-C–H functionalization and decarboxylative cross-coupling sequences would allow the use of benzoic acids as starting materials for the synthesis of complex molecules.[10] The high availability of benzoic acids renders these transformations very attractive.

Despite remarkable advances in both direct functionalization of C–H bonds and decarboxylative cross-coupling reactions, reactions that combine these two chemistries, that is, the decarboxylative cross-coupling of carboxylic acids with C–H bonds, are still scarce. The realization of this class of reaction would take advantage of both the high efficiency of C–H functionalization processes and the wide diversity of carboxylic acids, providing an attractive alternative to traditional metal-catalyzed cross-coupling reactions. Crabtree et al. reported, for the first time, four examples of C–H arylation reactions with 2,6-dimethoxybenzoic acid as an arylating reagent, which occurred under harsh conditions (200 °C) in low to moderate yields.[11] Later, Glorious et al. realized the intramolecular direct arylation of benzoic acids by tandem decarboxylation/C–H activation for the synthesis of dibenzofuran derivatives.[12] During the preparation of this manuscript, Larrosa et al. reported a Pd/Ag-catalyzed method for the intermolecular decarboxylative direct C3 arylation of indoles with electron-deficient benzoic acids.[13] This achievement by Larrosa and co-workers represented a big stride in the development of reaction involving C–H activation/decarboxylation sequences, nevertheless, there is still significant room for improvement with regard to the limited scope of benzoic acids. From the standpoints of both practical applications and fundamental research, the development of versatile catalysts for C–H arylation reactions with a broad range of benzoic acids as arylating reagents is highly desirable. To this end, we describe herein 1) the establishment of a versatile catalyst system that enables the use of both electron-rich and -deficient *ortho*-substituted benzoic acids as arylating reagents for the direct arylation of a variety of indoles, 2) demonstrate the high regioselectivity achieved in this reaction: 2-arylindoles were formed selectively from electron-rich benzoic acids and 3-arylindoles were generated exclusively from electron-deficient benzoic acids,[14] and 3) present the results of preliminary mechanism

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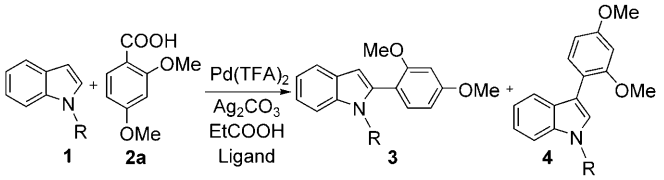
studies, which suggest that electron-rich and -deficient benzoic acids might take two different reaction pathways due to their difference in reactivity towards decarboxylation.

Initially, we examined the reaction of *N*-acetylindole **1** with 2,4-dimethoxybenzoic acid (**2a**; 2 equiv) in DMF at 80 °C in the presence of $Pd(TFA)_2$ (5 mol %, TFA = trifluoroacetate) as a catalyst, Ag_2CO_3 (2 equiv) as an oxidant and DMSO (3.5 equiv) as a ligand (1:70 ratio of Pd to DMSO), and observed that this reaction offered the desired C2-arylation product in 9 % yield (Table 1, entry 1). Under otherwise identical conditions, screening solvents showed that dioxane is the solvent of choice (Table 1, entry 2–4). The reaction conducted in dioxane exhibited a good selectivity at the 2-position of indole with an 8.0:1 C2/C3 ratio. Increasing the amount of DMSO to seven equivalents retarded the decarboxylation process and led to a decrease in yield (Table 1, entry 5). In contrast, when the amount of DMSO was reduced to one equivalent (1:20 ratio of Pd to DMSO), 2,4-dimethoxybenzoic acid smoothly underwent decarboxylation and provided an improved yield (Table 1, entry 6). Tetramethylene sulfoxide (TMSO) was observed to be more effective than DMSO (Table 1, entry 7). Although the use of one equivalent of DMSO or TMSO led to complete decarboxylation of **2a**, only moderate yields were obtained due to incomplete conversion of indole. We speculated that the introduction of additional carboxylic acids, such as propionic acid, to the reaction system would facilitate the electrophilic palladation on indole. As expected, the addition of propionic acid (0.25 equiv) gave rise to an improvement in yield (Table 1, entry 8). However, as the amount of propionic acid increased, the yield of the desired product decreased because too much propionic acid slowed decarboxylation. Interestingly, an increase in the amount of 2,4-dimethoxybenzoic acid not only promoted the conversion of indole but also improved the yield (Table 1, entry 10). Gratifyingly, further optimization disclosed that the treatment of *N*-acetylindole with 2,4-dimethoxybenzoic acid (5 equiv) in dioxane (1.5 mL) at 80 °C in the presence of $Pd(TFA)_2$ (7.5 mol %), Ag_2CO_3 (2 equiv), TMSO (1.5 equiv), and propionic acid (0.25 equiv) resulted in almost total conversion of indole, affording the desired product in 78 % yield with 16.4:1 C2/C3 ratio (Table 1, entry 13). The effect of an N-protecting group on the reactivity of indole has also been investigated under the optimal conditions. *N*-Pivaloylindole generated the corresponding product in a yield comparable to that of *N*-acetylindole with a lower selectivity (2.1:1 C2/C3 ratio), and *N*-tosylindole was less reactive than *N*-acetylindole, providing a moderate yield, whereas free *N*-H indole, *N*-methylindole, and *N*-*tert*-butyloxycarbonyl (Boc) indole gave no product.

Table 1. Optimization studies for Pd/Ag-catalyzed arylation of indoles(**1**) with 2,4-dimethoxybenzoic(**2a**).[a]

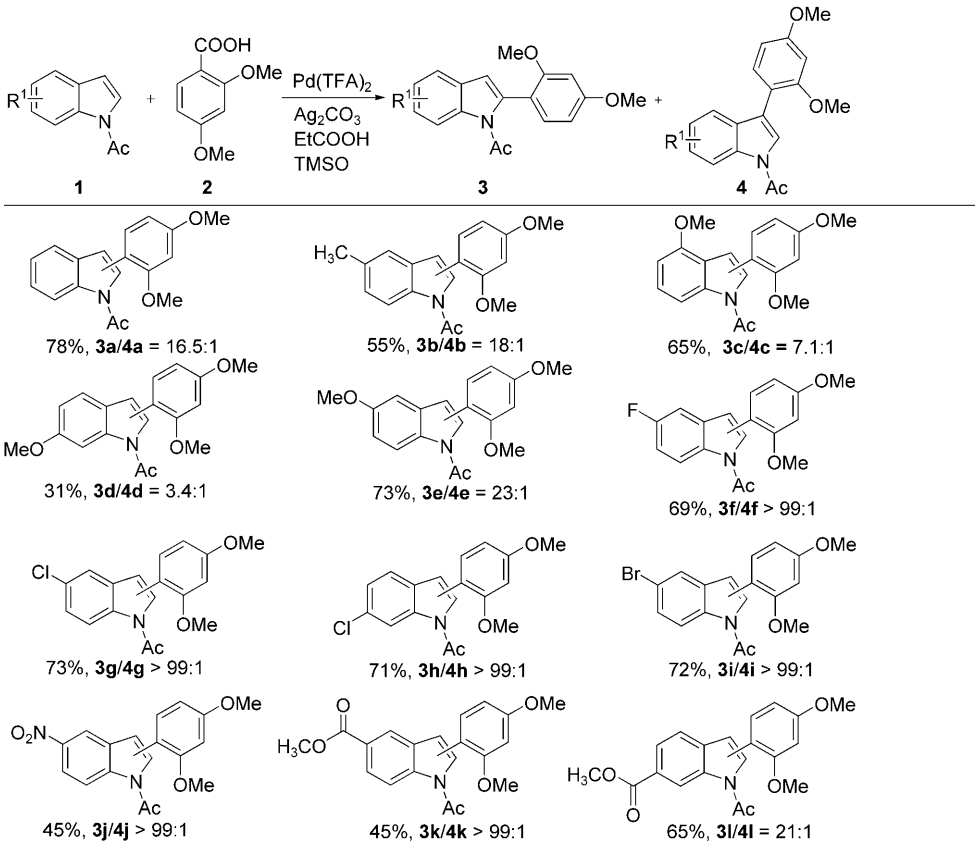


Entry	$Pd(TFA)_2$ [mol %]	**2a** [equiv]	R[b]	Solvent	Ligand ([equiv])	EtCOOH [equiv]	Yield [%][c]	Ratio (**3**/**4**)[d]
1	5	2	Ac	DMF	DMSO (3.5)		9	>99:1
2	5	2	Ac	dioxane	DMSO (3.5)		39	8.0:1
3	5	2	Ac	toluene	DMSO (3.5)		15	>99:1
4	5	2	Ac	NMP	DMSO (3.5)		4	>99:1
5	5	2	Ac	dioxane	DMSO (7.0)		26	10:1
6	5	2	Ac	dioxane	DMSO (1.0)		43	9.7:1
7	5	2	Ac	dioxane	TMSO (1.0)		49	11.4:1
8	5	2	Ac	dioxane	TMSO (1.0)	0.25	57	16.9:1
9	5	2	Ac	dioxane	TMSO (1.0)	1	49	20.4:1
10	5	4	Ac	dioxane	TMSO (1.0)	0.25	65	19.2:1
11	5	5	Ac	dioxane	TMSO (1.0)	0.25	33	>99:1
12	7.5	5	Ac	dioxane	TMSO (1.5)	0.25	70	17.4:1
13	7.5	5	Ac	dioxane[e]	TMSO (1.5)	0.25	78	16.4:1
14	7.5	5	H	dioxane[e]	TMSO (1.5)	0.25	0	
15	7.5	5	CH_3	dioxane[e]	TMSO (1.5)	0.25	<5	
16	7.5	5	Piv	dioxane[e]	TMSO (1.5)	0.25	72	2.1:1
17	7.5	5	Ts	dioxane[e]	TMSO (1.5)	0.25	42	>99:1
18	7.5	5	Boc	dioxane[e]	TMSO (1.5)	0.25	trace	

[a] Reaction conditions: indole (0.20 mmol, 1.0 equiv), Ag_2CO_3 (2 equiv), solvent (1.0 mL), 24 h, 80 °C. [b] Ac = acetyl, Piv = pivaloyl, Ts = tosyl, Boc = *tert*-butoxycarbonyl. [c] Isolated yields. [d] Determined by GC–MS. [e] Dioxane (1.5 mL).

With a set of optimized conditions in hand (Table 1, entry 13), we evaluated the scope of substituents on the *N*-acetylindole. As shown in Table 2, both electron-withdrawing and -donating substituents were compatible, affording synthetically useful yields in most cases. Importantly, high selectivity can be obtained for 2-arylindoles. Although substituents on the indole core can influence the yields of this reaction, no clear trend was observed for the dependence of the reaction yield on the nature of the substituents. For example, the electron-withdrawing fluoro-substituent at the C5-position provided a good yield (Table 2, **3f**), whereas electron-withdrawing nitro and ester groups at the 5-position of the indole core led to lower yields (Table 2, **3j**, **3k**). The position of the substituent on the indole core was also observed to affect both the reaction yield and selectivity, as illustrated by the reactions of three isomers of methoxy-substituted *N*-acetylindole (Table 2, **3c**–**e**). Notably, the reactions were tolerant of halogen substituents (Table 2, **3f**–**i**), providing the complementary platform for further transformations by Pd^0-catalyzed cross-coupling reactions.

Table 2. Reaction scope: Substitution on indole.[a]

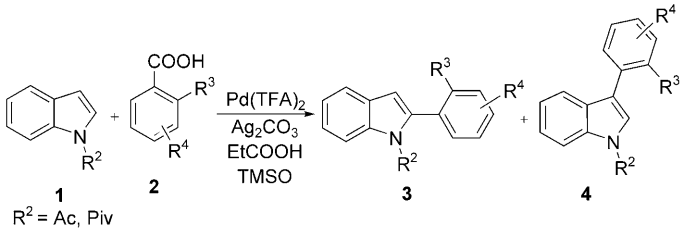


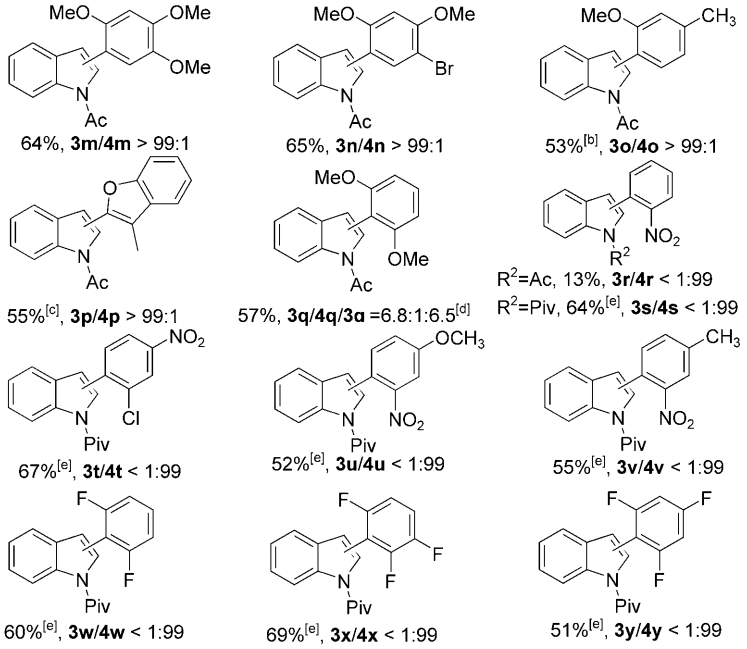
[a] Reaction conditions: indole (0.2 mmol, 1.0 equiv), benzoic acids (5.0 equiv), $Pd(TFA)_2$ (7.5 mol%), Ag_2CO_3 (2.0 equiv), EtCOOH (0.25 equiv), TMSO(1.5 equiv), dioxane (1.5 mL), 24 h, 80°C. The yields of **3** were isolated yields, the ratio of **3**/**4** was determined by GC–MS.

We next turned our attention to the reactions of various benzoic acids. Considering that varying the substituent of the benzoic acids directly gives rise to a change in acidity and decarboxylation rate, which would further affect the efficiency of cross-coupling reactions between indoles and benzoic acids, we reasoned that the reaction conditions should be adjusted to different benzoic acids to achieve efficient transformations. We were pleased to find that slight modifications of the optimal reaction conditions enabled the use of a variety of benzoic acids (Table 3). The optimal conditions obtained with 2,4-dimethoxybenzoic acid worked well for electron-rich benzoic acids (Table 3, **3m–q**). Due to low reactivity towards decarboxylation at 80°C, elevated temperature and a higher Pd loading were required to achieve good yields in the reactions involving 2-methoxy-4-methylbenzoic acid and 3-methylbenzofuran-2-carboxylic acid (Table 3, **3o**, **3p**). These reactions of electron-rich benzoic acids were observed to produce exclusively C2-arylation products. As an exception, the reaction of 2,6-dimethoxybenzoic acid, in which 7.5 equiv of propionic acid was required for reducing the rate of decarboxylative and activating indole, generated not only the regular product in 31% yield with 6.8:1 C2/C3 ratio but also **3a** in 26% yield (Table 3, **3q**). The product **3a** was likely to be formed from the Pd-catalyzed cross-coupling reaction of *N*-acetylindole with 1,3-dimethoxybenzene,[3a] which was generated in situ from the protodecarboxylatioon of 2,6-dimethoxybenzoic acid. In the cases of electron-deficient benzoic acids, *N*-pivaloylindole exhibited higher reactivity than *N*-acetylindole. The reactions of *N*-pivaloylindole with benzoic acids (3 equiv) conducted in DMF at 120°C in the presence of $Pd(TFA)_2$ (15 mol%), Ag_2CO_3 (3 equiv), TMSO (1.5 equiv), and propionic acid (0.25–1.5 equiv) gave the desired products in good yields (Table 3, **4s–y**). These reactions occurred exclusively at the C3-position of indole, exhibiting an inversion in regioselectivity compared with those of electron-rich benzoic acids. Since the reaction of electron-rich 2,4-dimethoxybenzoic acid with *N*-acetylindole in DMF predominately formed the C2-arylation product regardless of the presence or absence of propionic acid, and the reaction of *N*-acetylindole with electron-deficient 2-nitrobenzoic acid occurred exclusively at the C3 position of indole, we can rule out the possibilities that the nature of the solvent,[14a] the concentration of the carboxylic acids[14a] and the *N*-protecting groups[14b] are major factors controlling the regioselectivity of this reaction. Accordingly, we speculate that the high selectivity of this reaction may be closely related to the nature of the benzoic acids.

Although both experimental[5,6l] and theoretical studies[6j] established that $Pd(TFA)_2$ can efficiently promote the decarboxylation of electron-rich benzoic acids in the absence of other metal salts, studies by Larrosa et al. disclosed that $Pd(TFA)_2$ is incapable of catalyzing the decarboxylation of electron-deficient benzoic acids in DMSO at 120°C.[15a] The groups of Goossen[15b] and Larrosa[15a,c] independently demonstrated that silver salts are versatile catalysts for protodecarboxylation of a wide spectrum of benzoic acids. These previous results prompted us to investigate the roles of Pd and Ag in this Pd/Ag-catalyzed decarboxylative arylation of indoles. We observed that in the absence of Ag_2CO_3, stoichiometric amounts of $Pd(TFA)_2$ enabled the reaction of *N*-acetylindole with electron-rich 2,4-dimethoxybenzoic acid in dioxane at 80°C to generate arylindoles in 52% yield (5.9:1 C2/C3 ratio), accompanied by decarboxylative dimerization (**6a**, <5% yield) and protodecarboxylation of benzoic acid

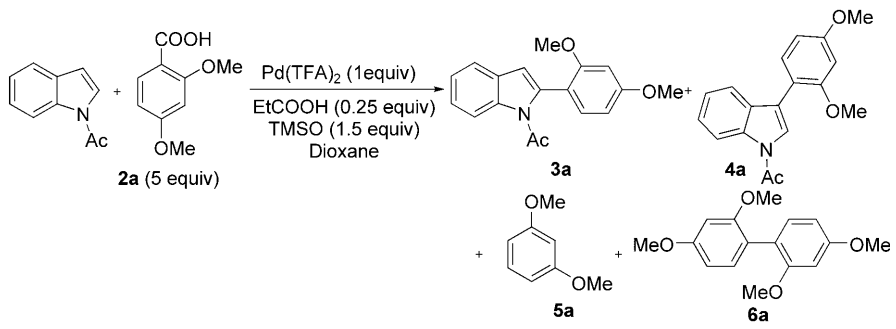
Table 3. Reaction scope with respect to benzoic acids.[a]



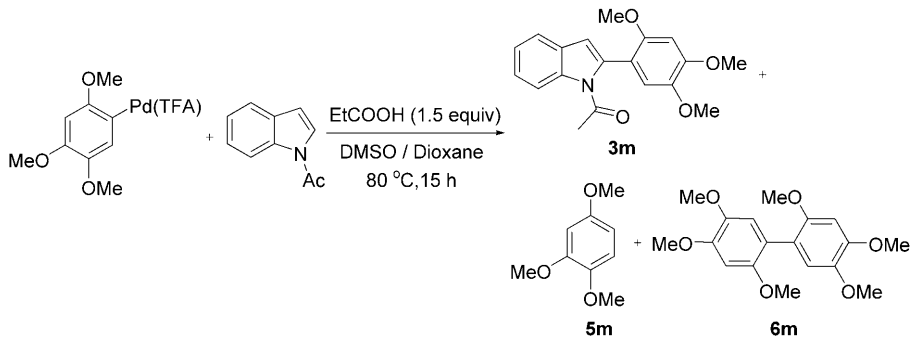


[a] Reaction conditions: indole (0.2 mmol, 1.0 equiv), $Pd(TFA)_2$ (7.5 mol%), Ag_2CO_3 (2 equiv), EtCOOH (0.25 equiv), TMSO (1.5 equiv), benzoic acids (5 equiv), dioxane (1.5 mL), 24 h, 80°C. The yields of **3** were isolated yields, the ratios of **3**/**4** were determined by GC–MS. [b] $Pd(TFA)_2$ (15 mol%), 140°C. [c] $Pd(TFA)_2$ (15 mol%), 100°C. [d] 7.5 equiv of EtCOOH. [e] $Pd(TFA)_2$ (15 mol%), Ag_2CO_3 (3.0 equiv), EtCOOH (1.5 equiv), TMSO (1.5 equiv), benzoic acids (2.5–3 equiv), DMF (1.5 mL), 24 h, 115–120°C.

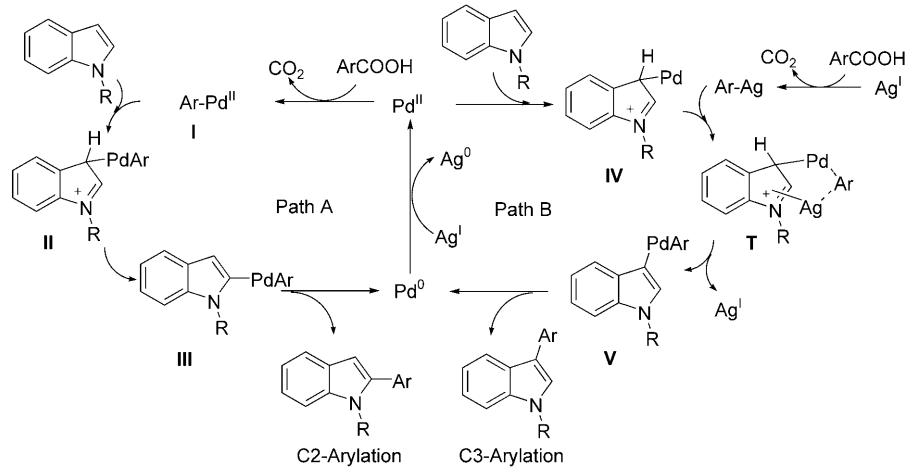
(**5a**, 62%) (Scheme 1). Furthermore, the arylpalladium(II) trifluoroacetate complex, which was generated from the decarboxylation of 2,4,5-trimethoxybenzoic acid by $Pd(TFA)_2$ in DMSO,[5c] was treated with a solution of an equivalent of *N*-acetylindole in dioxane and propionic acid (1.5 equiv) to generate 2-arylindole (**3m**) and 1,2,4-trimethoxybenzene (**5m**) in 13 and 51% yield respectively, accompanied by decarboxylative dimerization (**6m**, 11% yield) (Scheme 2), indicating that an arylpalladium intermediate can arylate indole by electrophilic palladation. In the absence of $Pd(TFA)_2$, the use of Ag_2CO_3 alone was ineffective for the decarboxylation of electron-rich 2,4-dimethoxybenzoic acid in dioxane, clearly illustrating that in the indole arylation reaction involving electron-rich benzoic acids Ag_2CO_3 was not responsible for the decarboxylation.[16] In the case of electron-deficient benzoic acids, however, the decarboxylation was observed to arise from Ag_2CO_3 rather than $Pd(TFA)_2$.[16] Based on these observations, we speculated that there might be two different catalytic pathways for the Pd/Ag-catalyzed decarboxylative arylation of indoles (Scheme 3). The reaction of electron-rich benzoic acid is thought to begin by the generation of arylpalladium intermediate **I** by Pd-promoted decarboxylation (path A). Next, the electrophilic attack of arylpalladium **I** on indole occurs at C3, where the electrophilic attack takes place preferentially, forming a C3-palladated species **II**. Following the migration of aryl–Pd fragment from C3 to C2, the deprotonation for rearomatization of indole leads to an intermediate **III** that further undergoes reductive elimination to release the cross-coupling product and Pd^0 species. The reoxidation of Pd^0 to Pd^{II} by Ag^I ion completes the catalytic cycle. In contrast, the reaction of electron-deficient benzoic acid might be initiated by the electrophilic palladation on indole and the formation of arylsilver complex by Ag-promoted decarboxylation, followed by transmetalation from Ag to Pd through transition-state complex **T** (similar complexes containing an iminium double bond coordinated to copper or ruthenium centers were also proposed as intermediates in the oxidative coupling reaction



Scheme 1.



Scheme 2.



Scheme 3. Two possible reaction pathways.

of amines[6m,17]) to form the Pd complex **V** that delivers C3 arylation product by reductive elimination (path B). If path B is operative, the coordination of Ag^I ion to C=N double bond in complex **T** might block the migration of the Pd fragment from C3 to C2, determining the C3 selectivity of this reaction.

In summary, the combination of $Pd(TFA)_2$, Ag_2CO_3, and propionic acid proved to be an efficient catalyst system for highly regioselective arylation of a wide range of indoles with both electron-rich and -deficient benzoic acids as arylating reagents, which provides an attractive complement to the existing methods for the direct arylation of indoles. Preliminary mechanistic studies suggested that the difference in reactivity towards decarboxylation between electron-rich and -deficient benzoic acids might result in two different catalytic pathways for the decarboxylative arylation of indoles, and therefore, leading to the inversion of the reaction regioselectivity. Current efforts are devoted to a more detailed mechanistic investigation and improvement of efficiency and substrate scope of this reaction.

Experimental Section

General procedure for decarboxylative cross-couplings of benzoic acids with indoles: All coupling reactions were performed on a 0.2 mmol scale (indole substrate) at 0.13 M unless otherwise stated. $Pd(TFA)_2$ (0.015–0.030 mmol, 7.5–15 mol%), indoles (0.2 mmol, 1 equiv), benzoic acid (0.5–1.0 mmol, 2.5–5 equiv), Ag_2CO_3 (0.4–0.6 mmol, 2–3 equiv), EtCOOH (0.0037 g, 0.05 mmol, 0.25 equiv; stored in 0.25 M dioxane or DMF), tetramethylene sulfoxide (0.0313 g, 0.3 mmol, 1.5 equiv) were weighed into a 25 mL glass vial. Dioxane (1.3 mL) or DMF (1.3 mL) was added. Then the mixture was heated under nitrogen for several hours. Upon completion, the crude reaction mixture was analyzed by GC–MS and showed a C2/C3 product distribution. Then the reaction mixture was diluted with ethyl ether (10 mL), filtered through a pad of silica gel, followed by washing with ethyl acetate (30 mL). The filtrate was washed with water (3×15 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel to provide the corresponding product.

Acknowledgements

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Keywords: decarboxylation · direct arylation · indoles · palladium · regioselectivity

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