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Rhodium-Catalyzed Decarbonylative Direct C2-Arylation of Indoles with Aryl Carboxylic Acids

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A Rh^{I}-catalyzed direct C2-arylation of indoles with diversely substituted aryl carboxylic acids has been developed using 2-pyrimidyl group as an easily installable and readily removable N-directing group. The reaction proceeded smoothly without the need for any external oxidants under relatively mild conditions to produce the C2-arylated indoles in high yields with excellent regioselectivity. A range of functional groups in both coupling partners were tolerated regardless of their electronic properties and positions. With the assistance of the 2-pyrimidyl group, these C2-functionalized products could further undergo C7-arylation to give the C7-aryl indole products. Mechanistic evidence supports that the reaction involves a decarbonylation step, and the carboxylic acids could be activated in situ by treatment with $(t\mathrm{BuCO})_2O$ to generate the active anhydrides.

The transition-metal-catalyzed C–C formation reaction that employs readily available carboxylates as carbon sources has become a valuable and promising access to functional molecules.[1] Since the pioneering reports by Trost and Chen,[2a] and Blaser and Spencer,[2b] the decarbonylative coupling reaction of carboxylates with olefins, alkynes, and organometallics has been investigated extensively.[3] Notably, carboxylic acids alone do not participate the coupling reaction, but they can be activated in situ by treatment with the less reactive carboxylic anhydride.[3d,4] To improve the atom economy and reaction efficiency, the combination of the decarbonylation of carboxylates with the direct functionalization of arene C–H bonds has drawn the attention of chemists.[5] Recently, the Rh-catalyzed decarbonylative intramolecular C–H arylation of 2-aryloxybenzoic acids was reported by Ryu and co-workers,[6a] and the use of Ac_2O as the activator of the carboxylic acids is necessary to drive the reaction. Shi and co-workers reported a $Rh^{I}/(t\mathrm{BuCO})_2O$ catalytic system that catalyzed the decarbonylative direct arylation of arenes efficiently with diversely substituted benzoic acids.[6b] The presence of a N-directing group and the use of bulky $(t\mathrm{BuCO})_2O$ as the activating reagent are critical for the catalysis. The broad substrate scope and wide functional-group tolerance make this approach a useful addition to the existing repertoire of decarboxylative direct arylations of arenes with benzoic acids.[7] Given the general utility of this methodology, it would be very attractive to explore its application in the direct arylation of aromatic heterocycles with aryl carboxylic acids.

The efficient and economical synthesis of functionalized indoles has long been a subject of considerable research interest because of the occurrence of such compounds in numerous natural products and biologically active molecules.[8] The recent research focus in this area has shifted to the direct functionalization of indoles without the need for prefunctionalized indole substrates.[9] Consequently, significant advances have been made in the direct arylation of indoles.[10,11] Notably, the direct decarboxylative arylation of N-protected indoles with widely commercially available aryl carboxylic acids could also be achieved successfully.[12] In 2009, Larrosa and co-workers first reported a Pd-catalyzed decarboxylative coupling of electron-deficient aryl carboxylic acids with N-pivaloyl indoles to afford C3-arylated products exclusively (Scheme 1 a).[12a] Shortly thereafter, Su and co-workers realized the Pd-catalyzed decarboxylative direct C2- or C3-arylation of indoles with benzoic acids by varying the nature of the benzoic acid and N substituent (Scheme 1 b).[12b] Unfortunately, these reported decarboxylative arylations relied on the use of *ortho*-substituted benzoic acids, and the use of *meta*- and *para*-substituted benzoic acids was largely underdeveloped. In consideration of the limitations of the reported catalysts and the appeal of decarbonylative catalysis, we initiated a program to investigate the catalytic decarbonylative direct arylation of heteroaryl compounds with aryl carboxylic acids. Herein we report that, in the presence of the Rh^{I} catalyst and an appropriate activator, *N*-(2-pyrimidyl)indoles could undergo highly efficient and selective decarbonylative C2-arylation with differently substituted aryl carboxylic acids in the absence of external oxidants under relatively mild conditions (Scheme 1 c).

In view of the influence of N-protecting groups to promote the direct C–H activation and functionalization of the C2-position of indoles,[9,10–13] we started our investigations by testing the reactions of a variety of N-protected indoles with benzoic acid **2 a** in toluene under the catalysis of $[Rh(CO)_2Cl]_2$ with $(t\mathrm{BuCO})_2O$ as the activator. *N*-(2-Pyrimidyl)indole (**1 a**) reacted

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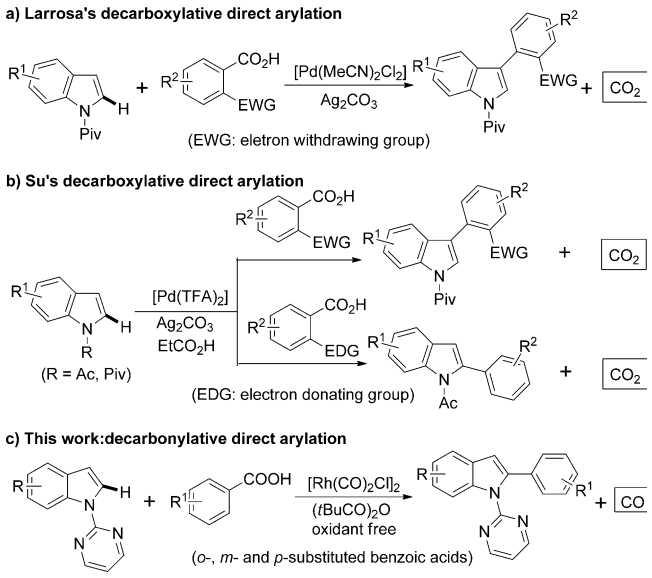
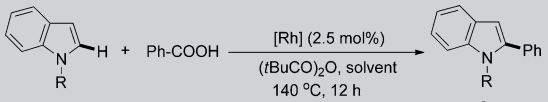


Scheme 1. Catalytic direct arylation of indoles with aryl carboxylic acids. Piv = Pivaloyl, TFA = Trifluoroacetyl, Ac = Acetyl.

smoothly with **2a** to afford the C2-arylated product **3aa** exclusively in 95% yield (Table 1, entry 1), and the C2-arylation of *N*-(2-pyridyl)indole (**1b**) gave the expected product **3ba** with a lower yield of 83% (Table 1, entry 2). Moreover, the attractiveness of the 2-pyrimidyl director also lies in that it could be installed and removed readily.[13] However, indole substrates with other N substituents, such as methyl, benzyl, acetyl, Boc, pivaloyl, and tosyl, and free N–H indole failed to furnish the desired products under otherwise identical conditions, which shows the importance of the directing group to successful arylation. With 2-pyrimidyl as the directing group, further screening established that *o*-xylene, PhCl, anisole, decalin, DMF, and DMSO were not suitable solvents (Table 1, entries 3–8). The subsequent optimization revealed that the use of $[Rh(CO)_2Cl]_2$ as a source of Rh is critical to secure a high catalytic performance, and diminished yields were obtained with other Rh precursors (Table 1, entries 9–14). We next examined the effects of various activators. Other activators, such as Boc_2O, Ac_2O, and $(MeOCO)_2O$, which are known to be capable to activate carboxylic acids in situ,[4,6a] were inefficient in the current study (Table 1, entries 15–17). The use of *t*BuCOCl as the activating reagent also decreased the reaction yield (Table 1, entry 18). Clearly, $(tBuCO)_2O$ is the best choice. The promoting effect of $(tBuCO)_2O$ in transition-metal-catalyzed coupling reactions of benzoic acids has been disclosed recently.[4b,c,e–h] The presence of an activator is indispensable as no reaction took place in its absence (Table 1, entry 19). A recent study by Ryu et al. showed that KI could promote the decarbonylation and intramolecular C–H arylation of 2-aryloxylbenzoic acids efficiently,[6a] but it was less effective in this case (Table 1, entry 20). A decrease of the reaction temperature disfavored the reaction, and the yield of **3aa** decreased to 73% at 120 °C (Table 1, entry 21). We also attempted to arylate both the C2- and C7-positions, but only **3aa** was isolated without the detection of the doubly arylated product (Table 1, entry 22). Notably, C3-arylation did not occur in any case.

Table 1. Optimization of the Rh-catalyzed direct arylation of indoles **1** with benzoic acid **2a**.[a]



1a-b **2a** **3**

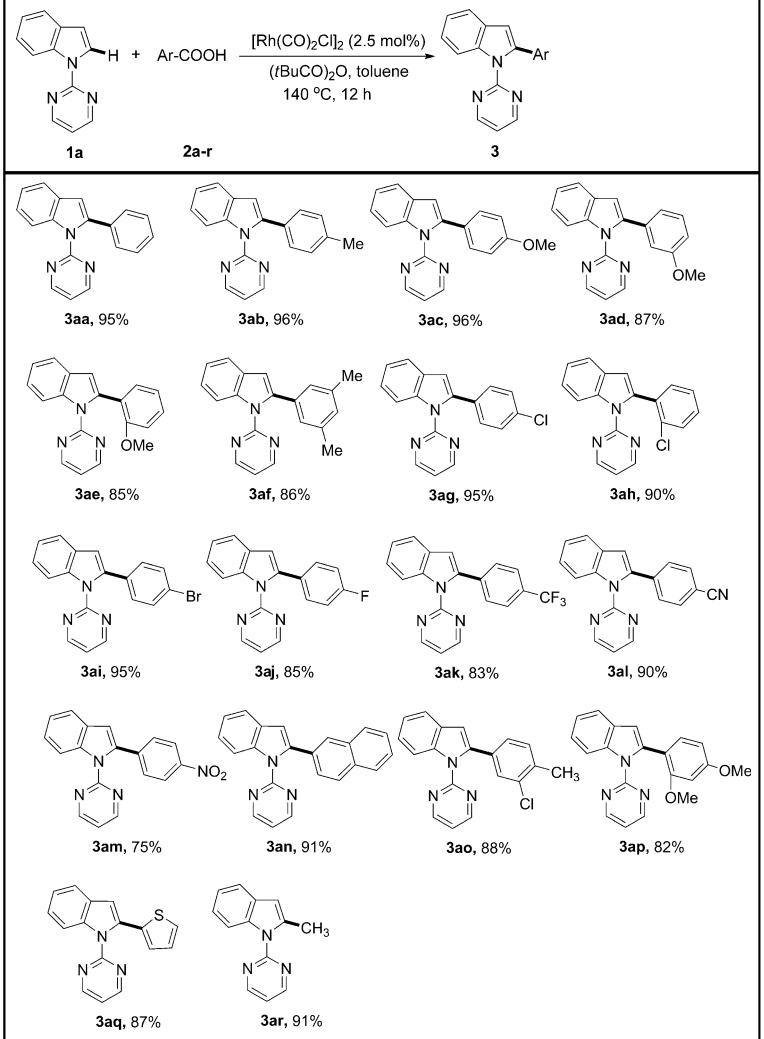
1a: R= 2-pyrimidyl
1b: R= 2-pyridyl

Entry	1	Rh precursor	Solvent	Yield [%][b]
1	**1a**	$[Rh(CO)_2Cl]_2$	toluene	95 (**3aa**)
2	**1b**	$[Rh(CO)_2Cl]_2$	toluene	83 (**3ba**)
3	**1a**	$[Rh(CO)_2Cl]_2$	*o*-xylene	90 (**3aa**)
4	**1a**	$[Rh(CO)_2Cl]_2$	PhCl	74 (**3aa**)
5	**1a**	$[Rh(CO)_2Cl]_2$	anisole	34 (**3aa**)
6	**1a**	$[Rh(CO)_2Cl]_2$	decalin	87 (**3aa**)
7	**1a**	$[Rh(CO)_2Cl]_2$	DMF	0 (**3aa**)
8	**1a**	$[Rh(CO)_2Cl]_2$	DMSO	0 (**3aa**)
9	**1a**	$[Rh(CO)_2(acac)]_2$	toluene	79 (**3aa**)
10	**1a**	$[Rh(cod)(OH)]_2$	toluene	68 (**3aa**)
11	**1a**	$[Rh(cod)Cl]_2$	toluene	76 (**3aa**)
12	**1a**	$[Rh(cod)_2]_2BF_4$	toluene	61 (**3aa**)
13	**1a**	$[Rh(1,5\text{-HD})Cl]_2$	toluene	70 (**3aa**)
14	**1a**	$[RhCp^*Cl_2]_2$	toluene	0 (**3aa**)
15[c]	**1a**	$[Rh(CO)_2Cl]_2$	toluene	76 (**3aa**)
16[d]	**1a**	$[Rh(CO)_2Cl]_2$	toluene	70 (**3aa**)
17[e]	**1a**	$[Rh(CO)_2Cl]_2$	toluene	0 (**3aa**)
18[f]	**1a**	$[Rh(CO)_2Cl]_2$	toluene	30 (**3aa**)
19[g]	**1a**	$[Rh(CO)_2Cl]_2$	toluene	0 (**3aa**)
20[h]	**1a**	$[Rh(CO)_2Cl]_2$	toluene	81 (**3aa**)
21[i]	**1a**	$[Rh(CO)_2Cl]_2$	toluene	73 (**3aa**)
22[j]	**1a**	$[Rh(CO)_2Cl]_2$	toluene	95 (**3aa**)

[a] Reactions were performed with **1** (0.5 mmol.), **2a** (0.75 mmol), catalyst (2.5 mol%), $(tBuCO)_2O$ (0.75 mmol), and solvent (3.0 mL) at 140 °C for 12 h. [b] Isolated yield. [c] Boc_2O was used as the activator.[d] Ac_2O was used as the activator. [e] $(MeOCO)_2O$ was used as the activator. [f] *t*BuCOCl was used as the activator. [g] No activator was added. [h] KI (50 mol%) was added. [i] Reaction temperature 120 °C. [j] **2a** (1.5 mmol) and $(tBuCO)_2O$ (1.5 mmol) were added. acac = Acetylacetonate, cod = 1,5-Cyclooctadiene, 1,5-HD = 1,5-hexadiene, Cp* = 1,2,3,4,5-pentamethylcyclopentadiene.

With the optimal reaction conditions in hand, we started to investigate the reaction of **1a** with a series of electronically and sterically diverse aryl carboxylic acids. The catalytic system worked effectively to afford the corresponding C2-arylated indoles in good to excellent yields, and all reactions exhibited excellent regioselectivities without the detection of C3-arylated products (Table 2). Notably, a variety of functional groups that include CH_3O (**3ac**, **3ad**, **3ae**, and **3ap**), F (**3aj**), CF_3 (**3ak**), CN (**3al**), and NO_2 (**3am**) were tolerated regardless of their electronic properties. Interestingly, the sensitive halogen substituent (Br and Cl) in the aromatic ring of aryl carboxylic acids survived well under the current conditions (**3ag**, **3ah**, **3ai**, and **3ao**). Meanwhile, 2-naphthoic acid (**2n**) also reacted well with **1a** to give the coupling product **3an** in 91% yield. Steric hindrance seems to have little influence on the reaction efficiency as aryl carboxylic acids that bear substituents at the 2-position showed good reactivity (**3ae**, **3ah**, and **3ap**). The reaction is not limited to aryl carboxylic acids only; heteroaryl carboxylic

Table 2. Rh-catalyzed direct arylation of **1a** with aryl carboxylic acids.[a,b]



[a] Reaction conditions: **1b** (0.5 mmol), **2** (0.75 mmol), $[Rh(CO)_2Cl]_2$ (2.5 mol%), $(tBuCO)_2O$ (0.75 mmol), toluene (3.0 mL), 140 °C, 12 h. [b] Isolated yield.

acids, such as 2-thiophenecarboxylic acid (**2q**), participated equally well to afford the corresponding product **3aq**. Acetic acid (**2r**) was a viable coupling partner to give the desired product **3ar** in 91% yield, but the reaction failed with other aliphatic carboxylic acids such as propionic acid and butyric acid.

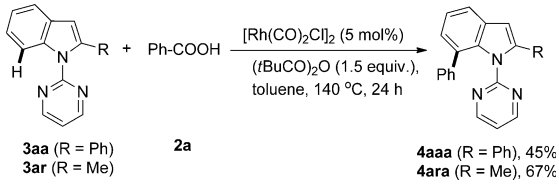
Next, we examined the reaction of other *N*-(2-pyrimidyl)indole derivatives with **2a**. The reaction is tolerant to a number of substituents on the benzene ring of indole moiety to provide the C2-arylated products (**3ca**–**3la**) exclusively in good to excellent yields (Table 3). Notably, the introduction of a substituent at the 3-position of the indole moiety has no marked impact on the reactivity, and the C3-substituted indoles (**1m**–**p**) reacted efficiently with **2a** to give the expected products (**3ma**–**3pa**) in good yields.

With the assistance of the pyrimidyl group, these C2-substituted indoles could undergo further arylation to give the C7-arylated products. The C7-arylation of **3aa** and **3ar** with **2a** was performed using 5 mol% $[Rh(CO)_2Cl]_2$ in 24 h to provide the desired products (**4aaa** and **4ara**) in satisfactory yields (Scheme 2).[14]

We also explored the coupling reaction of 2-(1*H*-pyrrol-1-yl)pyrimidine (**1q**) with aryl carboxylic acids (Scheme 3). It was found that **1q** was monoarylated effectively with **2a** to deliver the target product **3qa**, which could undergo further arylation with **2b** to give the biarylated product **4qab** [Scheme 3, (1)]. In the presence of five equivalents of **2a** and five equivalents of $(tBuCO)_2O$, the direct biarylation of **1q** was accomplished successfully to afford the biarylated product **4qaa** in 90% yield [Scheme 3, (2)].

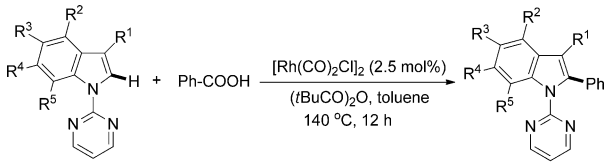
The removal of the pyrimidyl group from the coupling products was then attempted (Scheme 4). Deprotection was achieved easily by treating **3aa** and **3qa** with EtONa in DMSO at 100 °C,[6a] and the target products **5** and **6** were isolated in 89 and 94% yields, respectively.

Further investigations were undertaken to study the mechanism. On the basis of the reports of Yamamoto et al.,[4a,c,e,f] Goossen et al.,[4b,d,g–i] and Ryu et al.,[6a] it appears that the current reaction may proceed by the initial formation of acid anhydrides. Indeed, NMR spectroscopy revealed that the stirring of equimolar amounts of $(tBuCO)_2O$ and **2a** in toluene at 140 °C for 1 h resulted in a mixture of benzoic pivalic anhydride **7**, benzoic anhydride **8**, and $(tBuCO)_2O$ in a ratio of 1:0.35:0.6.[15] Compound **7** was then synthesized separately and subjected to the coupling reaction with **1a** under the catalysis of $[Rh(CO)_2Cl]_2$. The product **3aa** was formed exclusively in 90% yield in 12 h (Scheme 5a), which suggests that the Rh complex prefers to attack the less bulky part of the mixed anhydride to give the Rh-acyl intermediate because of the lack of steric hindrance. Commercially available **8** could also undergo the coupling reaction with **1a** to provide the product **3aa** in a high yield, but the reaction time could be shortened to 5 h (Scheme 5b). The higher reaction rate observed could be attributed to the higher stability of benzoate as the leaving group.[4g] Furthermore, $(tBuCO)_2O$ is completely unreactive under the current conditions (Scheme 5c). Clearly, anhydrides **7** and **8** generated in situ both contribute to the formation of arylation product **3aa**.[4g] Analysis of the gas phase of the reaction mixture using GC with thermal conductivity detection

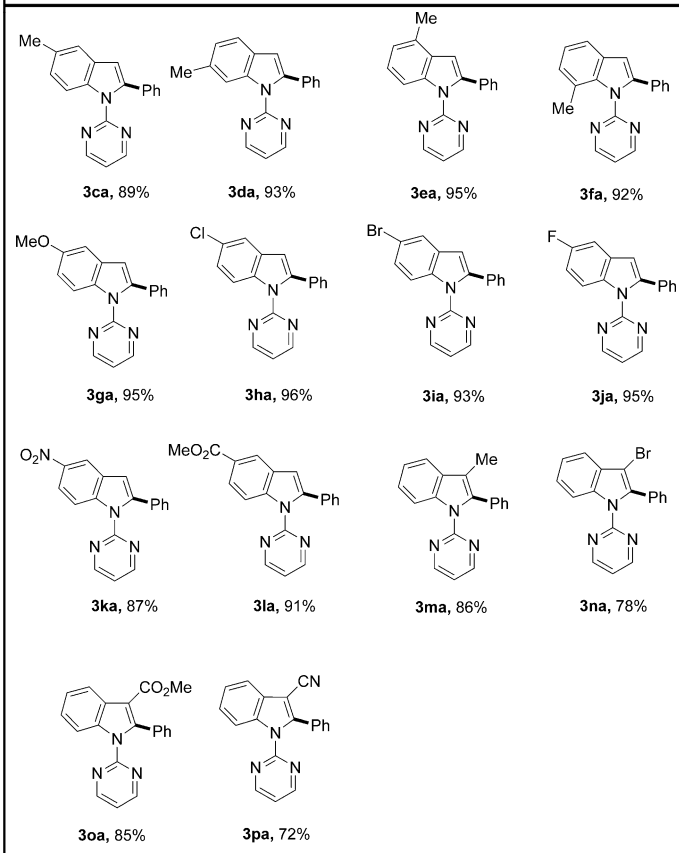


Scheme 2. Regioselective C7-arylation of indoles.

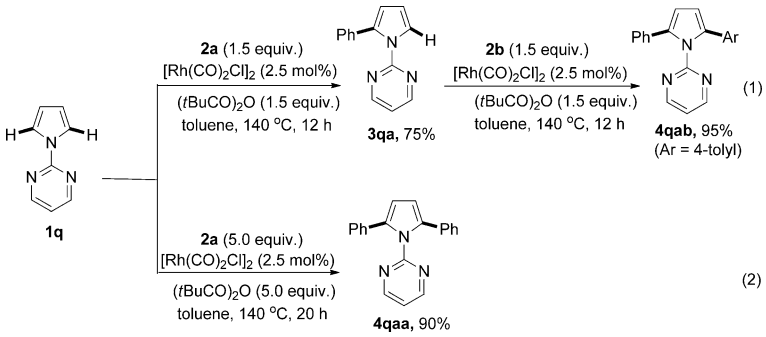
Table 3. Rh-catalyzed direct arylation of indoles with benzoic acid **2a**.[a,b]



1c-p 2a 3



[a] Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), $[Rh(CO)_2Cl]_2$ (2.5 mol%), $(tBuCO)_2O$ (0.75 mmol), toluene (3.0 mL), 140 °C, 12 h. [b] Isolated yield.



Scheme 3. Regioselective arylation of pyrroles.

(TCD) confirmed the generation of CO during the reaction, which indicates the involvement of a decarbonylation step in the current catalysis. On the basis of previous reports[3–6] and these observations, a plausible mechanism is suggested (Scheme 6). First, the reaction of the *N*-(2-pyrimidyl)-indole **1** with the Rh^I species produced the cyclorhodium intermediate **A** by C–H oxidative addition assisted by the pyrimidyl N atom. The anhydrides **B** and **C** that arise from the reaction of $ArCO_2H$ and pivalic anhydride reacted with **A** to give the intermediates **D** and **E** selectively, which yielded the intermediates **F** and **G** through decarbonylation. Reductive elimination of **F** and **G** furnished the desired product **3** and Rh^I was regenerated to complete the catalytic cycle.

In conclusion, we have described a general and efficient method to access C2-arylated indoles. In the presence of a $[Rh(CO)_2Cl]_2/(tBuCO)_2O$ catalytic system, a variety of commercially available aromatic carboxylic acids with different substitution patterns could undergo decarbonylative coupling reactions with *N*-(2-pyrimidyl)indoles to give the corresponding 2-aryl indole products exclusively in high yields. A diverse range of functional groups in both coupling partners was compatible with the reaction conditions. This methodology affords an attractive alternative that is complementary to the existing C–H arylations of indoles known in the literature.

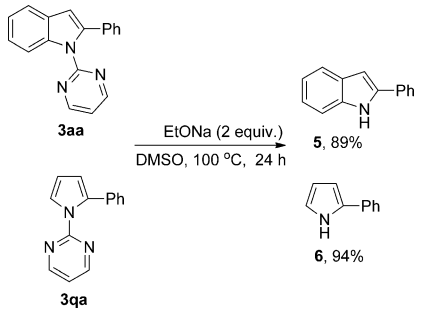
Experimental Section

General

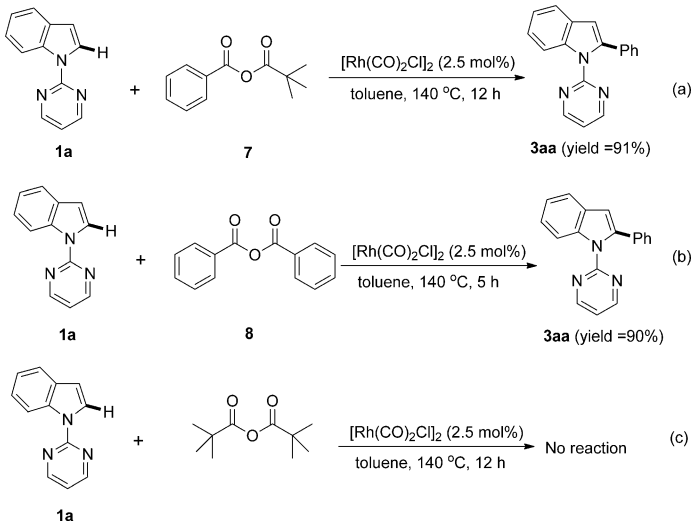
Unless otherwise noted, all experiments were performed under a N_2 atmosphere. ^1H and ^{13}C NMR spectra were recorded by using a Bruker Model Avance DMX 400 Spectrometer (^1H 400 MHz and ^{13}C 106 MHz, respectively). Chemical shifts (δ) are given in ppm and are referenced to residual solvent peaks, and coupling constants (J) are reported in Hz. The aryl carboxylic acids, catalysts, other common materials and solvents are commercially available and were used as received without further purification.

General Procedure for the direct arylation of indoles with aryl carboxylic acids

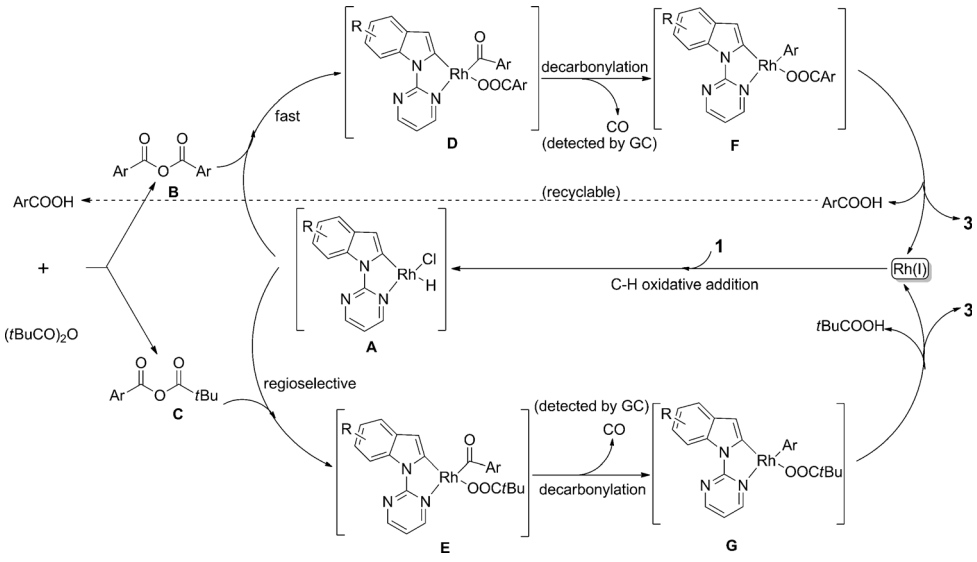
To an oven-dried pressure tube were added sequentially indole **1** (0.5 mmol), aryl carboxylic acid **2** (0.75 mmol), $[Rh(CO)_2Cl]_2$ (4.88 mg, 2.5 mol%), $(tBuCO)_2O$ (140.0 mg, 0.75 mmol), and anhydrous toluene (3.0 mL). After it was degassed three times, the tube was heated and stirred vigorously at 140 °C in an oil bath for 12 h under a N_2 atmosphere. Then the tube was removed from the oil bath and cooled to RT. The solvent was removed by vacuum evaporation, and the residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexane to give the pure product.



Scheme 4. Deprotection of the pyrimidyl group.



Scheme 5. Regioselective arylation with anhydrides.



Scheme 6. Proposed mechanism for the direct arylation of indoles.

Acknowledgements

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Keywords: anhydrides · carboxylic acids · oxidation · rhodium · synthesis design

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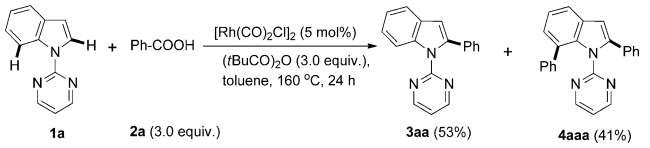

[15] After overnight stirring, the ratio became 1:0.375:0.6, and the mixed anhydride **7** is still present in the largest amount in the mixture.

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