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P(III)-Chelation-Assisted Indole C7-Arylation, Olefination, Methylation, and Acylation with Carboxylic Acids/Anhydrides *via* Rhodium Catalysis

Xiaodong Qiu[+], *Panpan Wang*[+], *Dingyi Wang, Minyan Wang, Yu Yuan, and Zhuangzhi Shi**

Abstract: *Rhodium-catalyzed C7-selective decarbonylative arylation, olefination and methylation of indoles with carboxylic acids or anhydrides via C-H and C-C bond activation have been developed. Furthermore, C7-acylation products can also be generated selectively at a lower reaction temperature in our system. The key to the high reactivity and regioselectivity of this transformation is the appropriate choice of an indole N-P^{t}Bu$_2$ chelation-assisted group. This method has many advantages, including easy access and removal of the directing group, the use of cheap and widely available coupling agents, no requirement of an external ligand or oxidant, a broader substrate scope, high efficiency and the sole regioisomer.*

As a heteroaromatic scaffold frequently found in natural products, pharmaceuticals and biologically active compounds, indole-nuclei-containing structures have garnered tremendous attention over the past century.[1] In this context, the regioselective functionalization of indole C-H bonds has long attracted the interest of synthetic chemists.[2] To date, the C-H functionalization of indole at the C3 or C2 position has been successfully achieved by transition metal catalysis.[3] Due to the inherent reactivity of the pyrrole side of the indole, the development of methodologies to control the positional selectivity on the benzenoid core has remained a great challenge.[4] Traditional methods to synthesize indole C7-linkage natural compounds mainly rely on the prefunctionalization of the C7 position in the form of leaving groups (e.g., Br, OTf, BR$_2$, SnR$_3$)[5] with coupling partners using transition metal catalysis. For instance, a palladium-mediated intramolecular Stille reaction between the 7-stannylindole and iodoarene was used a key step in total synthesis of Chloropeptin I as an anti-HIV agent (Figure 1a).[5b] Remarkably, a smart biosynthetic way to prepare such indole C7-linkage cyclic peptides has evolved in nature. In the biosynthesis of streptide, a covalent linkage formed directly between the C7 position of indole and the side chains of lysine by enzyme StrB.[6] Inspired by this biochemical process, the development of a unified way to directly and selectively access the indole C-H bond at the C7 position for diverse transformations without prefunctionalization is extremely meaningful.

Selective C-H activation of indole at the C7 position is achieved by installing the substituents at the C2 or C3 position to block the reactivity at this side[7] or using indoline as a precursor.[8] Recently, some elegant methods have been developed by utilizing the C7-selective directing groups.[9] In 2016, we developed a P(V) directing group (*N*-P(O)^{t}Bu$_2$) that is able to perform Pd(II)-catalyzed oxidative Suzuki coupling at the C7 position of indoles with aryl boronic acids by O atom coordination in the presence of stoichiometric heavy metal salts including Ag$_2$O, Cu(OTf)$_2$, and CuO as the co-oxidants.[10] Recently, our group also reported the rational design of a P(III) directing group (*N*-P^{t}Bu$_2$) that directs C7-alkylation and arylation of indoles with olefins and (hetero)aryl bromides *via* rhodium catalysis.[11] This P(III) group opens a door for C7 selective C-H functionalization of indoles. Herein, we describe the development of the decarbonylative cross-couplings[12] of carboxylic acids or anhydrides with indoles at the C7 position by P(III)-chelation-assisted Rh(I)-catalyzed C-H and C-C bond activation. The indole P(III) atom binds to the Rh center and selectively delivers the catalyst to the C7 position, which subsequently undergoes decarbonylative arylation, olefination, and methylation. In addition, the decarbonylation process can also be suppressed at a lower reaction temperature to yield indole C7-acylation products.[13]

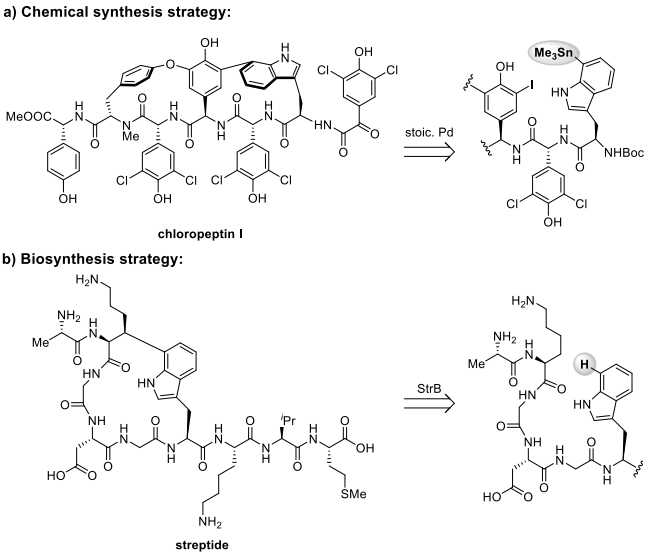

Figure 1. Comparing chemical synthesis and biosynthesis of indole C7-linkage cyclic peptides.

Our investigation commenced with the decarbonylative cross-coupling of *N*-P^{t}Bu$_2$ indole **1a** and benzoic anhydride (**2a**) to yield C7-phenylation product **3aa** (Table 1). The best results were obtained with a catalytic amount of [Rh(cod)Cl]$_2$ and NaHCO$_3$ as a base in toluene within 12 h at 150 °C without any external ligands or oxidants. Under these conditions, conversion was completed with a 99% yield of the desired product **3aa** (entry 1). Other rhodium complexes such as [Rh(CO)$_2$Cl]$_2$ and Rh(cod)$_2$OTf were less efficient for this reaction (entries 2-3). A control experiment revealed that the cross-coupling process does not occur in the absence of the rhodium catalyst (entry 4). Using Na$_2$CO$_3$ as the additive led to slight erosion in yield (entry 5). Under these conditions, when PhCOOH (**2a'**) was employed as a phenyl source with (^{t}BuCO)$_2$O, the conversion was poor (entry 6); however, a significant improvement in conversion was observed by using

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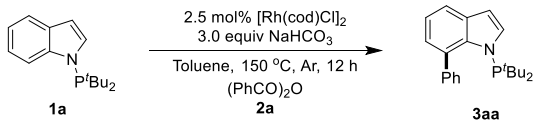
Table 1. Reaction development.[a]



Entry	Variation from the "standard conditions"	Yield of **3aa** (%)[b]
1	none	99 (95)[c]
2	$[Rh(CO)_2Cl]_2$ instead of $[Rh(cod)Cl]_2$	62
3	$Rh(cod)_2OTf$ instead of $[Rh(cod)Cl]_2$	48
4	without $[Rh(cod)Cl]_2$	0
5	Na_2CO_3 instead of $NaHCO_3$	85
6	PhCOOH (**2a'**) + Boc_2O instead of **2a**	16
7	PhCOOBoc (**2a''**) instead of **2a**	65
8	at 130 °C	79

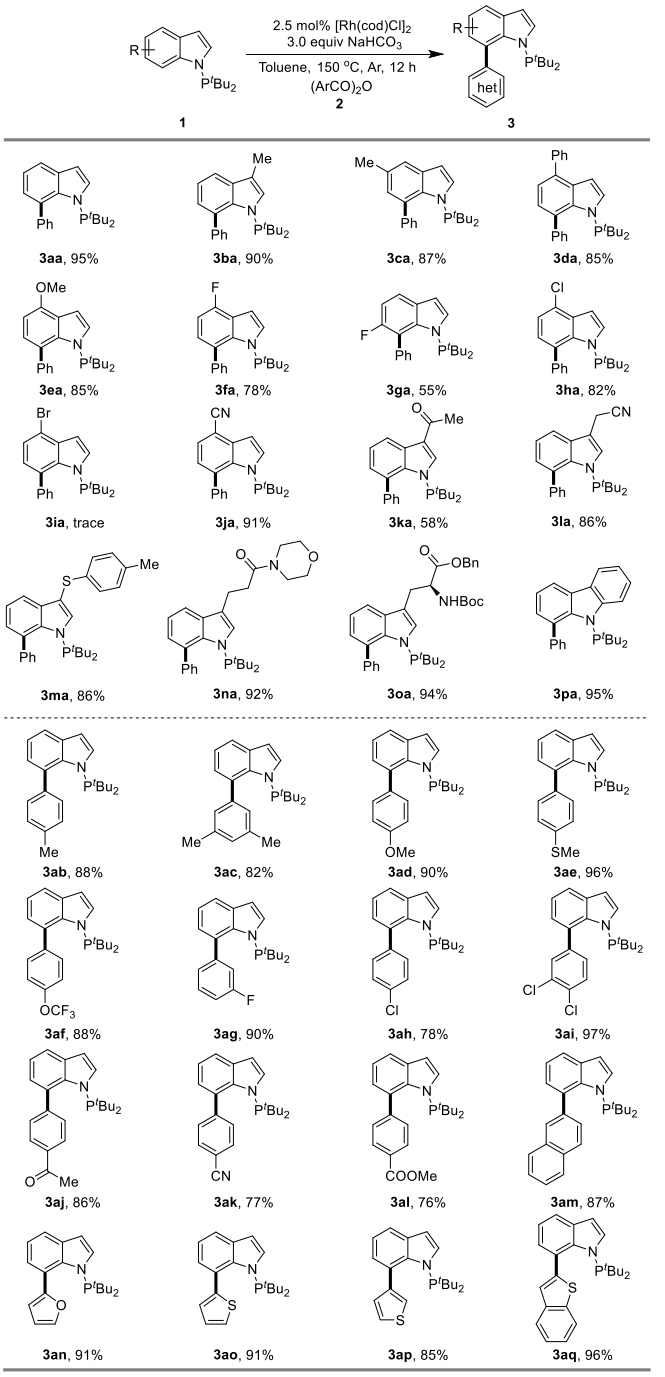
[a] Conditions: **1a** (0.20 mmol), **2** (0.30 mmol), base (3.0 equiv), solvent (1.0 mL), 24 h, under Ar. [b] Determined by GC analysis. [c] Isolated yield.

PhCOOBoc (**2a''**) in this reaction (entry 7). Finally, lowering the temperature to 130 °C had a substantial impact on the reaction outcome (entry 8).

With the best conditions identified, we first examined the scope of this P(III)-directed C7-arylation process (Table 2). Decarbonylative cross-coupling reactions of benzoic anhydride (**2a**) with a broad range of *N*-P^{t}Bu$_2$ indoles were first examined. Indoles bearing electron-neutral and donating substituents including methyl (**3ba-3ca**), phenyl (**3da**), and methoxy (**3ea**) at the C3-C5 positions underwent facile olefination affording the corresponding products in good to excellent yields. The halogen-containing motifs such as F (**3fa-3ga**) and Cl (**3ha**) work very well in the C7-olefination; however, an indole with a Br-substituent such as **1i** gave a trace amount of product **3ia**. Indole substrates containing electron-deficient substituents such as a cyano (**3ja**) group were also converted in good efficiency. Substrates with strong chelation-ability groups at the C3 position such as acetyl (**3ka**), cyanomethyl (**3la**), *p*-tolylthio (**3ma**) and amide (**3na**) were significantly tolerated with good C7-selectivity, and C4-arylation products were not observed. In particular, the treatment of tryptophan derivative **1o** under standard conditions provided 7-phenyl tryptophan derivative **3oa** in excellent yield. In addition to indole, P(III)-protected carbazole can also be converted into product **3pa** in 73% yield. We also examined the scope of different carboxylic acid anhydrides with indole **1a**. The functional group compatibility of this method was nicely illustrated by the fact that Me (**3ab-3ac**), OMe (**3ad**), SMe (**3ae**), OCF_3 (**3af**), F (**3ag**), Cl (**3ah-3ai**), Ac (**3aj**), CN (**3ak**), COOMe (**3al**) at aryl motif of carboxylic acid anhydride and 2-naphthoic anhydride (**3am**) could all be equally accommodated. Moreover, a series of heteroarenes such as furan (**3an**), thiophene (**3ao-3ap**), and benzothiophene (**3aq**) could also be installed to the C7 position of indole.

The decarbonylative reaction was further optimized with cinnamic acid (**4a**) as a partner to produce the indole C7-olefination products,[8b, 9b] avoiding the use of the noncommercially available cinnamic acid anhydride (Table 3). We found that the reaction reached the optimal efficiency and selectivity with 2.5 equiv of Boc_2O in the presence of 5.0 mol % of $Rh(cod)_2OTf$ as catalyst. Product **5aa** was obtained in 93% yield of at 120 °C for 18 h under argon atmosphere. As shown, all indole and carbazole substrates shown in arylation reaction could be applied in C7-olefination reactions (**5ba-5pa**). Under these reaction conditions, the Br-substituted indole **1i** was compatible affording the desired product **5ia** in 81% yield. Notably, the Boc group in tryptophan product **5oa** (54%) was deprotected during the olefination process. A wide range

Table 2. Scope of the P(III)-directed C7-arylation of indoles.[a]



[a] Conditions: **1a** (0.20 mmol), **2** (0.30 mmol), $[Rh(cod)Cl]_2$ (2.5 mol%), $NaHCO_3$ (3.0 equiv) in toluene at 150 °C, 12 h, under Ar.

of cinnamic acids that incorporate electron-neutral, electron-donating and electron-withdrawing substituents on arenes were readily tolerated as well (**5ab-5aj**). Among them, the structure of product **5ag** was confirmed by X-ray analysis. In addition, naphthalene substrates (**5ak-5al**) were also shown to exhibit high levels of reactivity. However, some vinyl carboxylic acids including *trans*-2-pentenoic acid (**4m**) and fumaric acid monomethyl ester (**4n**) did not work in our system.

Methylation is fundamental in medicinal chemistry, which can have a profound influence on biologically active molecules.[14] Typical methods to form a methylarene involve strong nucleophiles or strong and often toxic electrophiles. We were excited to find that, the P(III)-directed decarbonylative methylation could also occur using the inexpensive and nontoxic acetic anhydride as a

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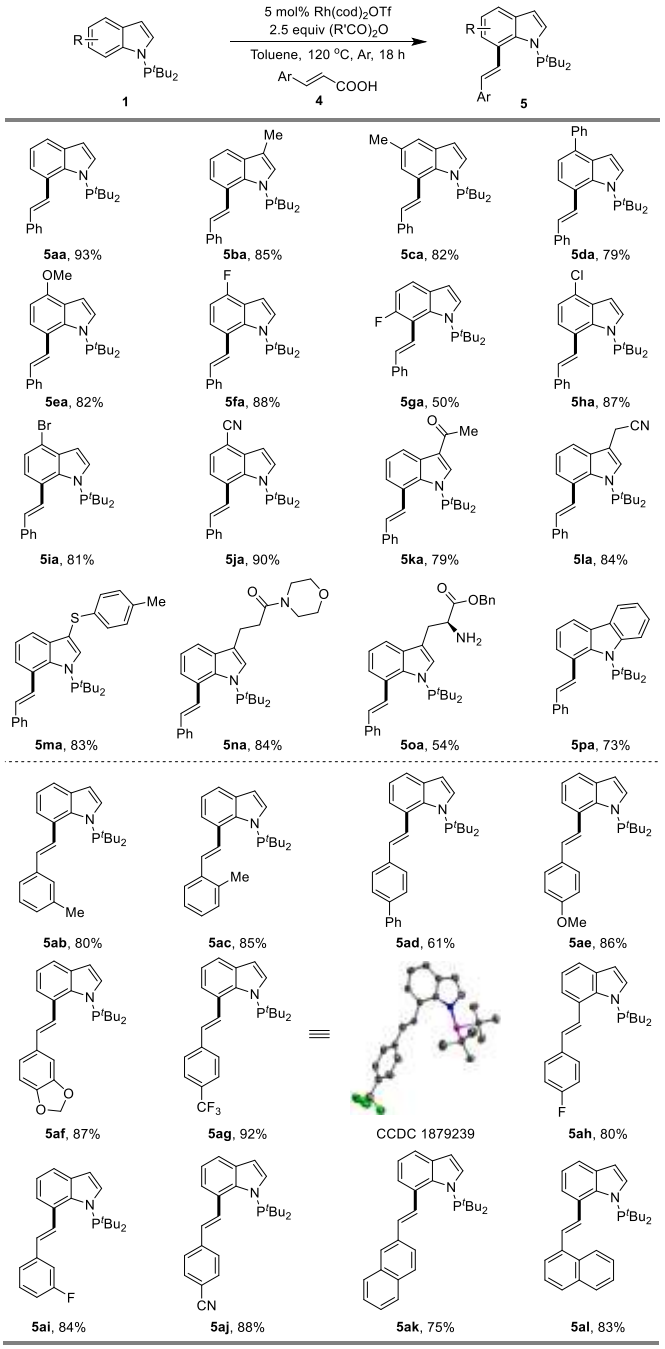
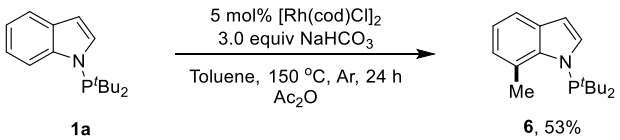
Table 3. Scope of the P(III)-directed C7-olefination of indoles.[a]



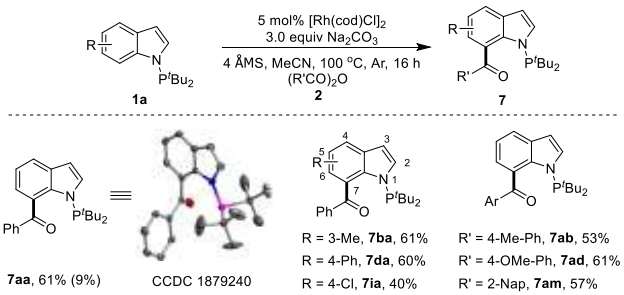
[a] Conditions: $Rh(cod)_2OTf$ (5.0 mol%), **1** (0.20 mmol), **4** (0.50 mmol), $(R'CO)_2O$ (0.50 mmol) in toluene at 120 °C, 18 h, under Ar, for **4a**, using Boc_2O (0.50 mmol); for **4b**-**4l**, using methacrylic anhydride (0.50 mmol).

methylating reagent, the desired C7-methylation product **6** was formed in 53% yield at current reaction conditions (Scheme 1).



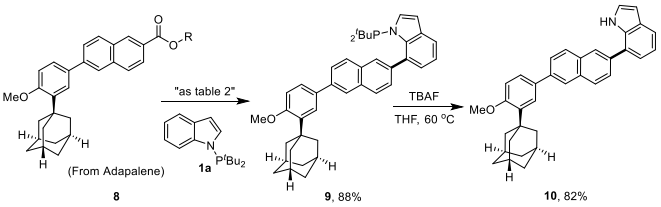
Scheme 1. P(III)-Directed C7-methylation of indole **1a**.

The reaction of indoles with carboxylic anhydrides in the presence of Lewis acids, Friedel-Crafts acylation, is widely known as a general method for the C3-acylation of indoles.[15] The decarbonylation process of carboxylic anhydrides can be significantly suppressed at a lower reaction in a slightly modified P(III)-directed system, and indole acylation products can be generated, unlike the regioselectivity of traditional Friedel-Crafts methods (Scheme 2). C7-acylation product **7aa** was obtained at 100 °C for 16 h with a trace amount of decarbonylative byproduct **3aa** (9%), which was also confirmed by X-ray analysis. Other indoles such as **1b**, **1d** and **1i**, and carboxylic anhydrides such as **2b**, **2d** as well as 2-naphthoic anhydride **2m** can undergo C7-acylation to obtain the corresponding aromatic ketone products in 40-61% yields.



Scheme 2. P(III)-Directed C7-acylation of indoles.

This P(III)-directed cross-coupling reaction was also viable with late-stage modification (Scheme 3). For example, anhydride **8** derived from Adapalene, a second-generation topical retinoid primarily used in the treatment of mild-moderate acne, can be subjected to decarbonylative C7-arylation with indole **1a** to produce the product **9** in 88% isolated yield. Furthermore, this directing group can be easily removed by TBAF in THF, and 82% of *N*-free indole **10** was isolated.



Scheme 3. P(III)-Directed late-stage modification.

Although the detailed mechanism of the reaction remains unclear, we propose a tentative catalytic cycle as shown in Figure 2.[16] Rhodium **A** coordinates first to the P(III) atom of the indole **1**, leading to the formation of complex **B**. A reversible cyclometalation through an anion-assisted deprotonation[17] at the indole C7 position

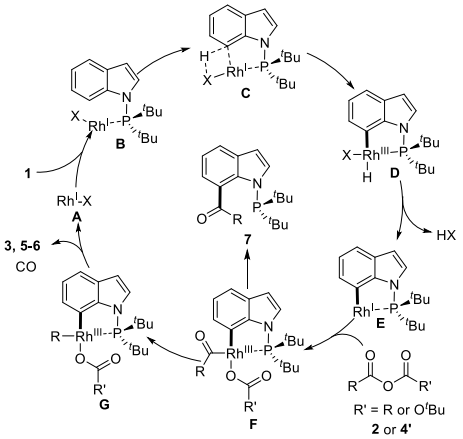


Figure 2. Plausible reaction mechanism.

delivers the intermediate **C**, which induces oxidative addition to generate the $Rh^{III}H$ species **D**.[11a] Elimination of intermediate **D** gives the rhodacycle **E**. Then oxidative addition of the carboxylic anhydrides **2** or **4'** to **E** affords the intermediate **F**. Subsequent decarboxylation can yield the rhodium species **G**. Further reductive elimination and dissociation delivers the final products and regenerates the active catalyst. At a lower temperature, decarboxylation can be inhibited from acylrhodium complex **F** affording the acylation products by reductive elimination.[18]

In summary, we have reported an efficient C7-selective direct arylation, olefination, methylation and acylation of indoles with the aid of the P(III)-directed group by rhodium catalysis. The reaction employed commercially available carboxylic acids or anhydrides, does not require the addition of an exogenous ligand, and is applicable to the coupling of a variety of indoles. These present results represent an important discovery that is expected to be substantially extended to other new transformations.

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Keywords: Indoles ·arylation ·olefination ·methylation ·acylation

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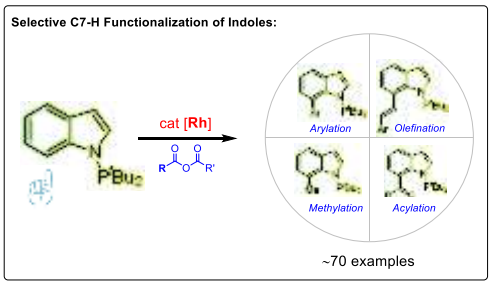
P(III)-Chelation-Assisted Indole C7-Arylation, Olefination, Methylation, and Acylation with Carboxylic Acids/Anhydrides via Rhodium Catalysis



4 in 1: P(III)-chelation-assisted group coordinates to the rhodium(I) catalyst and undergoes C-H activation at indole C7-position, which then allows for a series of selective C-H functionalization with carboxylic acids or anhydrides.