ORGANIC CHEMISTRY

Rhodium-catalyzed, P-directed selective C7 arylation of indoles

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The indole scaffold will continue to play a vital role in the future of drug discovery and agrochemical development. Regioselective direct arylation of indoles on the benzenoid moiety is a challenging task due to the inherent reactivity of the C2 and C3 positions. Here, we have developed an effective strategy for the regioselective direct arylation of indoles at the C7 position with (hetero)aryl bromides by the rational design of a directing group. The key to the high selectivity and reactivity of this method is the appropriate selection of a class of directing groups, N-PR$_2$ (R = ^{t}Bu and ^{c}Hex), that are easily removed in the presence of the Wilkinson's catalyst. Using the present method as a key step, formal synthesis of marine alkaloid dictyodendrin B has also been demonstrated.

INTRODUCTION

The indole motif is a ubiquitous feature in bioactive natural products and represents an important structural fragment in the pharmaceutical and agrochemical fields (*1*). Many useful processes exist for the modification of the indole structure, and transition metal–catalyzed coupling reactions are of particular use (*2*–*4*). Driven by the principles of atom and step economy, there is continuing interest in the C–H functionalization (*5*–*10*) of indoles. Since the pioneering work of Sames and co-workers on the selective direct C2 arylation of indoles (*11*, *12*), remarkable progress has been made in this field, and palladium has featured prominently in the developments. In 2006, Sanford and co-workers reported a Pd-catalyzed direct arylation of indoles with diaryliodonium salts that afforded 2-arylindoles in high yields under mild reaction conditions (*13*). Later, the Fagnou group reported a breakthrough in Pd-catalyzed selective dehydrogenative cross-coupling reactions of indoles and simple arenes for the formation of 3-arylindoles (*14*). After several years of effort, direct and site-selective arylations of indoles at the C2 and C3 positions have been solved by various novel strategies from many research groups including those of Lautens (*15*), DeBoef (*16*), Gaunt (*17*), Shi (*18*), Larrosa (*19*), Glorius (*20*), Greaney (*21*), and Ackermann (*22*). However, the methods of selective C–H functionalization, especially for direct arylation of the benzene core of an indole, have been a challenge to develop due to the inherent reactivity of the C2 and C3 positions (*23*).

7-Arylindoles are key building blocks in several biologically active compounds, including the dictyodendrin alkaloids (*24*), the pyrrolophenanthridine (*25*) family, and the macrocyclic polypeptide chloropeptin (Fig. 1A) (*26*). Previously, in the total syntheses of these natural products, prefunctionalized starting materials such as 7-borylindole (*27*) and 7-stannylindole (*28*) were used to construct the 7-arylindole moieties. Typically, selective C–H functionalization of an indole at the C7 position requires substituents at the C2 position to block the reactivity at this site (*29*). In 2010, Hartwig and co-workers developed an efficient, iridium-catalyzed C–H borylation without a blocking group at the C2 position in which the regioselectivity was controlled by an *N*-silyl directing group (*30*). The corresponding arylation products can be further derivatized via tandem Suzuki-Miyaura coupling reactions (*27*). Later, other groups also reported C7 arylations of indoles that generated the desired products via the indoline intermediate; in these methods, the reduction of the indoles was followed by directed C–H arylation and subsequent reoxidation to the indole structure (*31*). In 2016, we also developed Pd(II)-catalyzed direct arylation of indoles with arylboronic acids at the C7 position using a sterically hindered *N*-P(O)^{t}Bu$_2$ directing group (*32*). With the aid of oxygen coordination, this reaction has an excellent regioselectivity, but indoles and aryl boronic acids containing cyano, amide, nitro, and mercapto groups and heteroaryl boronic acids were found to be ineffective. Moreover, using the strong reducing agent ($LiAlH_4$) for directing group removal leads to many functional groups such as aldehyde, carbonyl, carboxylic acid, and ester, which are not compatible for this step. In addition, the reaction requires large amounts of Ag_2O (2.0 equiv), CuO (1.0 equiv), and $Cu(OTf)_2$ (0.5 equiv) as the co-oxidants. Nevertheless, methods for the direct C7 arylation of indoles are still in their infancy in terms of scope and practicality.

The fundamental challenges in enhancing the reactivity and site selectivity associated with the C–H activation reactions can be efficiently addressed by using substrates with a robust directing group capable of precoordinating the metal catalyst (*33*). These directors are usually nitrogen- and oxygen-containing functional groups. Phosphine-metal complexes are usually quite stable and difficult to dissociate. As a result, the docking of a metal to a phosphorous atom in a catalytic C–H activation process is rare (*34*–*38*). Guided by this rationally designed method, here we developed a strategy for the C7 arylation of indoles through rhodium-catalyzed, phosphorous-directed C–H arylation reactions (Fig. 1B). The installation of a tertiary phosphine group on the *N* atom of an indole could selectively deliver the rhodium center to the C–H bond at the C7 position of the indole and allow the subsequent direct arylation. The remarkable selectivity stems from the formation of a five-membered metalacycle through C–H bond cleavage at the C7 position, which is favored over the formation of the four-membered metalacycle at the C2 position. This method tolerates a broad range of indoles and (hetero)aryl bromides containing a wide range of functional groups with various steric and electronic properties. The formed products can act as key intermediates in total syntheses of indole alkaloids. Inspired by a series of indole-based commercially available ligands (Fig. 1C) (*39*, *40*), this method also provides an efficient method for the rapid construction of C7-arylindole–based *N*-PR^2 ligand libraries. Moreover, the

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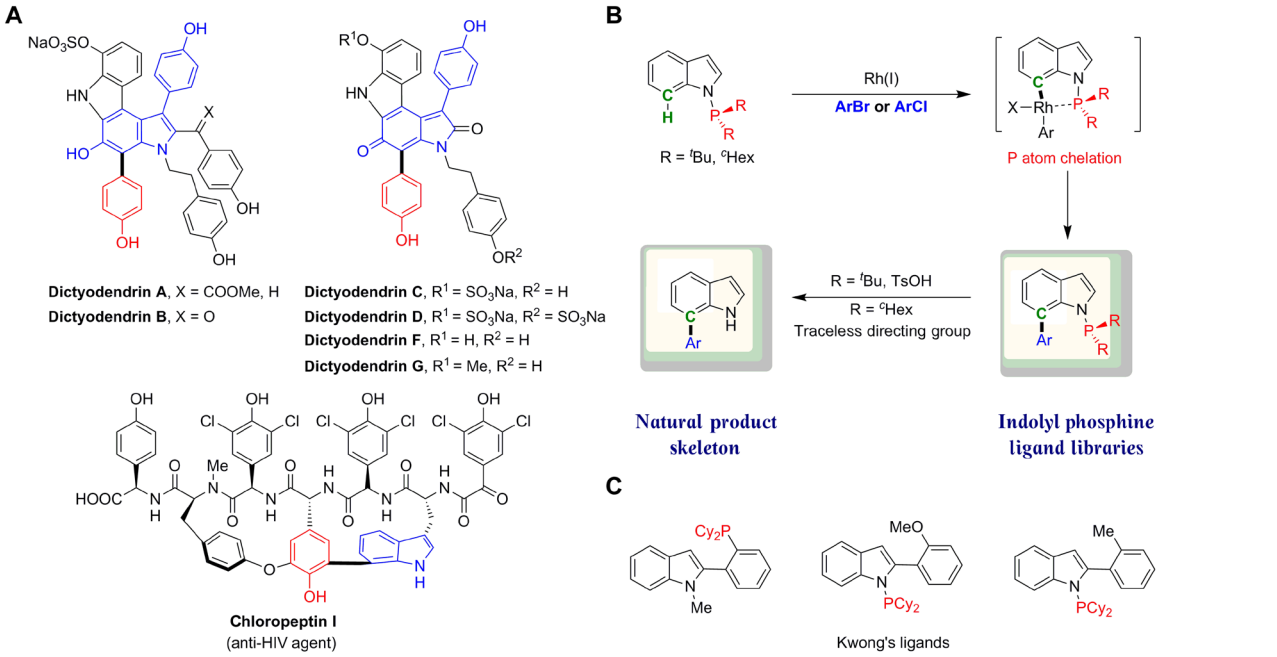


Fig. 1. Development of a Rh(I)-catalyzed protocol for the P-directed C7 arylation of indoles. (**A**) Nature products containing 7-arylindole moiety. (**B**) Rh(I)-catalyzed, phosphorous-directed C7 arylation of indoles. (**C**) Indole-based commercially available ligands.

synthetic applications and plausible mechanism of the current reaction have been evaluated. In total, these studies have not only greatly improved the synthetic use of C–H activation reactions for the preparation of 7-arylindoles but also significantly increased the understanding and broadened the applications of Rh(I)-catalyzed, tertiary phosphine-directed C–H arylations.

RESULTS

Reaction condition optimization

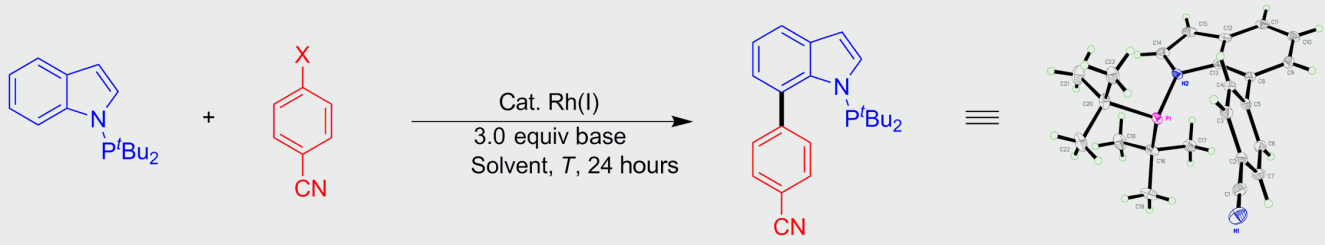
To establish a platform for this chemistry, we initially selected the cross-coupling of *N*-P^{t}Bu$_2$ indole (**1a**) with 4-bromobenzonitrile (**2a**), as shown in Table 1. The Pd-catalyzed direct C7 arylation of (4-cyanophenyl)boronic acid with *N*-P(O)^{t}Bu$_2$ indole under our previously reported conditions provided only a trace amount of the desired product. By using 6.0 mole percent (mol %) of Rh(PPh$_3$)$_3$Cl as the catalyst and 3.0 equiv of Cs_2CO_3 as a base in toluene at 110°C, we observed C7-arylated product **3aa** in 10% yield (entry 1). Somewhat unexpectedly, when we switched the base to ^{t}BuOLi, the yield markedly increased to 84% (entries 2 and 3). The solvent effect was not pronounced, and the reaction in *m*-xylene led to a full conversion of the indole and 94% yield of **3aa** (entries 4 to 6). Notably, lowering the reaction temperature to 80°C did not have a substantial impact on the reactivity, and the reaction afforded the desired product in 96% yield (entries 7 and 8). Less expensive aryl chlorides remain challenging substrates in traditional cross-coupling processes. To our delight, this C–H arylation reaction catalyzed by the Wilkinson's catalyst provided a high conversion of aryl chloride **2a′** and afforded the desired product in 84% yield (entry 9). In contrast, aryl iodide **2a″** only generated a trace amount of product **3aa** (entry 10). Under these conditions, when 1.0 to 3.0 mol % catalyst loading was used, the conversions were still appreciable (entries 11 and 12). Control experiments revealed that switching from the Wilkinson's catalyst to other rhodium salts such as [Rh(cod)Cl]$_2$ resulted in lower conversions (entries 13 and 14), and in the absence of the rhodium catalyst, the coupling process does not occur (entry 15).

Scope of the methodology

With the optimized conditions in hand, we first examined the scope of indole **1a** with various (hetero)aryl bromides for the direct indole C7 arylation process (Table 2). Bromobenzene (**2b**) and its derivatives containing electron-donating and electron-withdrawing substituents such as methyl (**3ac**), methoxy (**3ad** to **3af**), mercapto (**3ag**), halogen-containing (CF_3, F, and Cl; **3ah** to **3am**), cyano (**3an** to **3ap**), and amide (**3aq**) groups were tolerated in this reaction. Among these reactions, the reaction of ortho-substituted aryl bromides [e.g., 2-bromobenzonitrile (**2n**)] was sluggish under the present conditions presumably due to steric reasons. In particular, aryl bromide **2q** can be used for the selective C–H arylation of the indole target, and the catalyst does not bind with the amide directing groups. 2-Bromonaphthalene (**2r**) also works very well in this reaction. 5-Bromo-1-methyl-indole (**2s**) is an important coupling partner since it shows that two indoles that are differentially protected can be selectively coupled. Other heteroaryl bromides, such as quinolone (**2t**) and pyridine (**2u**), were all coupled with excellent regioselectivities in 62 to 93% yields.

Next, cross-coupling reactions of 4-bromobenzonitrile (**2a**) with a broad range of *N*-P^{t}Bu$_2$ indoles were examined. Indoles bearing electron-neutral and electron-donating substituents including methyl (**3ba** to **3da**), phenyl (**3ea**), and methoxy (**3fa** to **3ga**) groups at the 3 to 5 positions underwent facile arylation and afforded the corresponding products in excellent yields. C6-substituted indole **1g**, which contains a substituent that can sterically block the C7 position, also delivered coupled product **3ga** in good yield, although the reaction

Table 1. Reaction optimization. Reaction conditions: **1a** (0.20 mmol), **2** (0.30 mmol), base (3.0 equiv), solvent (1.0 ml), 24 hours, under Ar. CCDC, Cambridge Crystallographic Data Centre.



1a **2** **3aa** CCDC 1838725

1	X	[Rh] (mol %)	Base	Solvent	*T* (°C)	Yield (%)*
1	Br (**2a**)	$Rh(PPh_3)_3Cl$ (6.0)	Cs_2CO_3	Toluene	110	10
2	Br (**2a**)	$Rh(PPh_3)_3Cl$ (6.0)	^{t}BuONa	Toluene	110	33
3	Br (**2a**)	$Rh(PPh_3)_3Cl$ (6.0)	^{t}BuOLi	Toluene	110	84
4	Br (**2a**)	$Rh(PPh_3)_3Cl$ (6.0)	^{t}BuOLi	PhCl	110	89
5	Br (**2a**)	$Rh(PPh_3)_3Cl$ (6.0)	^{t}BuOLi	$PhCF_3$	110	91
6	Br (**2a**)	$Rh(PPh_3)_3Cl$ (6.0)	^{t}BuOLi	*m*-Xylene	110	94
7	**Br (2a)**	**$Rh(PPh_3)_3Cl$ (6.0)**	**^{t}BuOLi**	***m*-Xylene**	**80**	**96**
8	Br (**2a**)	$Rh(PPh_3)_3Cl$ (6.0)	^{t}BuOLi	*m*-Xylene	60	15
9	Cl (**2a′**)	$Rh(PPh_3)_3Cl$ (6.0)	^{t}BuOLi	*m*-Xylene	110	84
10	I (**2a″**)	$Rh(PPh_3)_3Cl$ (6.0)	^{t}BuOLi	*m*-Xylene	110	Trace
11	Br (**2a**)	$Rh(PPh_3)_3Cl$ (3.0)	^{t}BuOLi	*m*-Xylene	80	81
12	Br (**2a**)	$Rh(PPh_3)_3Cl$ (1.0)	^{t}BuOLi	*m*-Xylene	80	64
13	Br (**2a**)	$[Rh(cod)Cl]_2$ (3.0)	^{t}BuOLi	*m*-Xylene	80	11
14†	Br (**2a**)	$[Rh(cod)Cl]_2$ (3.0)	^{t}BuOLi	*m*-Xylene	80	64
15	Br (**2a**)	–	^{t}BuOLi	*m*-Xylene	80	0

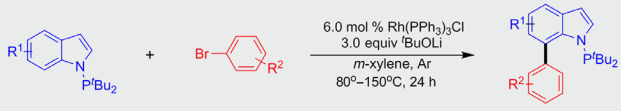
*Isolated yields. †With 10 mol % PPh_3.

required a higher temperature. In particular, halogen-containing motifs (F, Cl, and Br; **3ha** to **3ma**) work very well in the C7-selective arylation, which highlights the potential use of this process in combination with further conventional cross-coupling transformations. An indole substrate bearing a cyano group at the C3 position was efficiently converted to **3na**, but the yield of the highly electron-deficient 5-nitro-1*H*-indole derivative (**1o**) was noticeably lower. In addition, tryptamine derivative **1p** and 3-indolepropionic acid amide (**1q**) were compatible with the reaction conditions and afforded corresponding products **3pa** and **3qa** in 52 and 72% yields, respectively. We were very pleased to see that this method could be applied to more challenging substrates. *N*-P^{t}Bu$_2$–substituted 4-azaindole (**1r**) could also be converted into arylated product **3ra** in 83% yield as a single regioisomer. Carbazole (**1s**) is also well tolerated in this Rh(I)-catalyzed arylation reaction, and it affords ortho-arylated product **3sa** as the sole product in 81% yield. 3,3′-Diindolylmethane (DIM) is found in cruciferous vegetables such as broccoli, brussels sprouts, cabbage, and kale and exhibits various potential anticancer properties (*41*). By instilling two *N*-P^{t}Bu$_2$ directing groups, the dual direct arylation of 3,3′-dindolylmethane derivative **1t** readily provided 7,7′-diarylated indole **3ta** in 60% yield. These products highlight the power of the present direct arylation reaction, as conventional methods do not allow such facile syntheses of these materials.

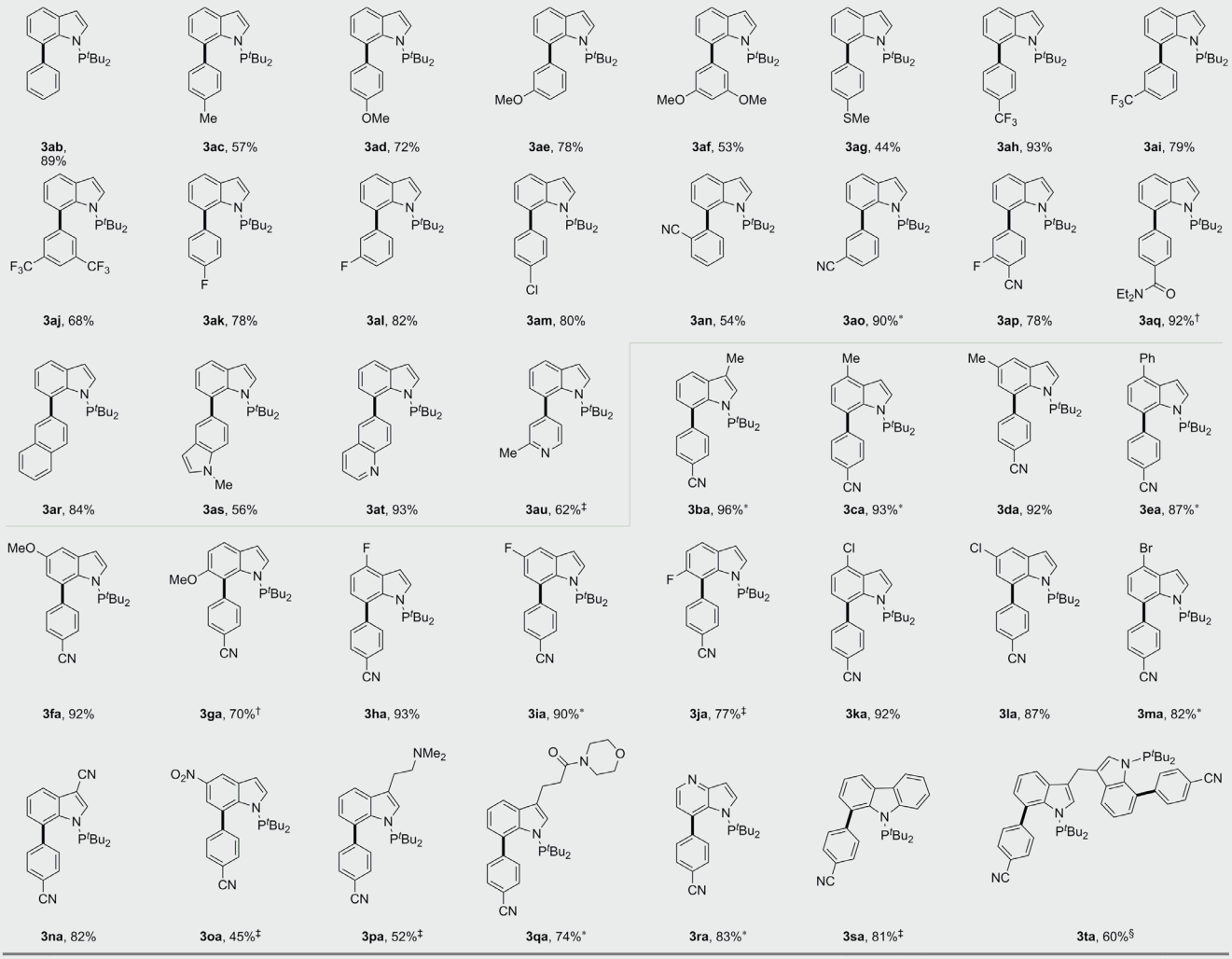
The *N*-P^{t}Bu$_2$ directing group can be easily removed by treatment with TsOH·H_2O. As shown in Fig. 2, a 74% overall yield was obtained in three steps for the conversion of the 1*H*-indole to 7-aryl indole **4aa** (the installation of the directing group was nearly quantitative, the C7 arylation with 4-bromobenzonitrile occurred in 96% yield, and the removal of the directing group occurred in 78% yield). These results demonstrated that the functional group compatibility of the directing group removal step, and our first-generation method, which used a strong reducing agent ($LiAlH_4$) to remove the directing group, would not be compatible with such functional groups.

Although this tertiary phosphine-directed arylation can achieve the desired transformations with high reactivity and selectivity, the indole *N*-P^{t}Bu$_2$ group requires additional removal steps. This limitation can be overcome by using a traceless directing group that is more easily cleaved from the products (*42*). The coupling of *N*-P^{c}Hex$_2$ indoles **1′** with aryl bromides was achieved by using the same reaction conditions in the presence of a rhodium catalyst. To our delight, this *N*-P^{c}Hex$_2$ group showed promising results, and it can be removed by subjecting the crude product to silica gel or treating it with dilute acid during workup (Table 3). It was found that a wide range of bromoarenes bearing various substituents produced corresponding 7-aryl-1*H*-indoles **4** in good yields. This traceless directing group strategy enabled the preparation of different C7-arylated indoles **4aa** to **4ub** with various

Table 2. Scope for the *N*-P^{t}Bu–directed C7-(hetero)arylation of indoles. Reaction conditions: **1a** (0.20 mmol), **2** (0.40 mmol), $Rh(PPh_3)_3Cl$ (6.0 mol%), LiO^tBu (3.0 equiv) in *m*-xylene (1.0 ml) at 150°C, 24 hours, under Ar, isolated yields.



1 + 2 → 3



*80°C. †100°C. ‡130°C. §Using **1t** (0.10 mmol), **2** (0.40 mmol), $Rh(PPh_3)_3Cl$ (12.0 mol%), and LiO^tBu (6.0 equiv) in *m*-xylene (1.0 ml) at 100°C.

substituents at the C3 to C6 positions in moderate to good yields. Notably, other directing groups such as *N*-PPh_2 (**1a**″) were also investigated, but none of desired product **3aa**″ was detected (see fig. S1).

Synthetic applications

Since the isolation of the dictyodendrin family of marine alkaloids (dictyodendrins A to E) in 2003 by Fusetani and Matsunaga (*43*), they have attracted the attention of the scientific community due to their unique potential at telomerase inhibitors in cancer chemotherapy (*44*). In 2012, dictyodendrins F to J were isolated by Capon *et al.* from the southern Australian marine sponge *Ianthella* sp (*45*). To date, these complex indole alkaloids have inspired a number of elegant total syntheses from several groups (*27*, *46*–*52*). The installation of the 4-methoxyphenyl group at the C7 position of the indole framework is one of the key steps during the total synthesis. To test the reliability of our method, we applied it to the rapid construction of a key indole intermediate **8** in the synthesis of dictyodendrin B (Fig. 3). We prepared indole substrate **6** from inexpensive substrate **5** according to Dong's method (*53*). P^cHex_2 protection of compound **6** gave key substrate **7a** in 92% yield. According to this new generation strategy, the C7-selective direct arylation of compound **7a** with 4-bromoanisole successfully afforded coupling product **8** in 72% yield (*48*). Notably,

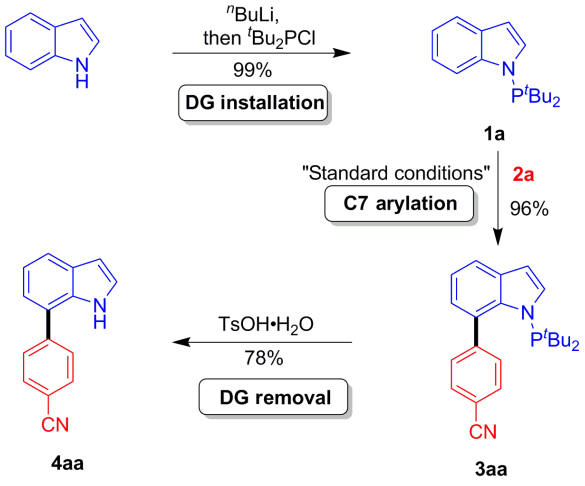


Fig. 2. Relevant steps in overall transformation. Reaction conditions: **1a** (0.20 mmol), **2** (0.40 mmol), $Rh(PPh_3)_3Cl$ (6.0 mol%), and LiO^tBu (3.0 equiv) in *m*-xylene (1.0 ml) at 150°C, 24 hours, under Ar. DG, directing group.

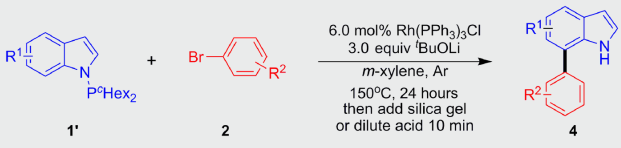
the application of the first-generation method only generated a trace amount of the desired product **8′** from indole **7b**. This example demonstrates that this new strategy for the direct arylation of the indole C7 position is well suited to the rapid and modular construction of complex molecules from minimally functionalized and widely available aromatic precursors. We envision that this efficient method could be used for the diversity-oriented synthesis of dictyodendrin derivatives for future medicinal applications.

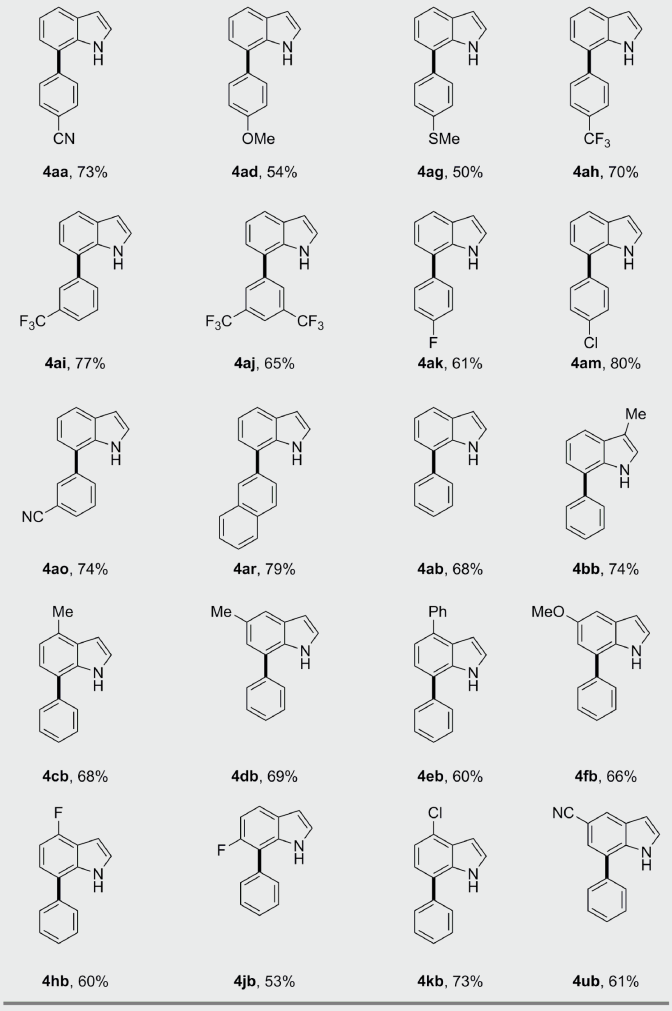
We also tested some of our newly constructed indolyl *N*-P^tBu_2 ligands in Suzuki-Miyaura coupling reactions. In the Pd-catalyzed coupling of 1-chloro-4-methylbenzene (**9**) with phenyl boronic acid (**10**), C7-aryl indole ligands with different steric and electronic properties provided **11** in 62 to 94% yields, while parent ligand **1a** only gave the desired product in 59% yield. These comparative results demonstrate the crucial role of the aryl ring directly attached to the C7 position of the indole scaffold. On the basis of the simplicity of the ligand synthesis as well as the simplicity of modifying the ligand skeleton, we anticipate that further enhancements in the reactivity and versatility of the C7-aryl indolyl *N*-P^tR_2 ligand series are attainable (Fig. 4).

DISCUSSION

To get insight into the reaction mechanism, we carried out deuteration experiments with a stoichiometric amount of $Rh(PPh_3)_3Cl$ and ^{t}BuOLi in D4-MeOH. ^{1}H nuclear magnetic resonance (NMR) analysis revealed that deuteration at the C3 position of **1a** gradually increased over time, and 67% deuterium incorporation was observed, respectively, after 20 hours. Under these conditions, no D/H exchange was detected in the absence of ^{t}BuOLi or Wilkinson's catalyst, suggesting that base-assisted metalation occurs at the C7 position with the aid of the P^tBu_2 directing group (Fig. 5A). Moreover, the obvious D/H exchange was also detected when the reaction of indole D7-**1a** was carried out in the presence of the methanol. This result indicates that the C–H cleavage is reversible under catalytic conditions (Fig. 5B). In addition, the KIE (kinetic isotope effect) value of the C–H activation process was 1.2, revealing that the C–H cleavage is fast and not involved as a rate-determining step (Fig. 5C) (*54*–*57*).

Table 3. Scope for the *N*-P^cHex–directed C7 arylation of indoles. Reaction conditions: **1** (0.20 mmol), **2a** (0.40 mmol), $Rh(PPh_3)_3Cl$ (6.0 mol %), and LiO^tBu (3.0 equiv) in *m*-xylene (1.0 ml) at 150°C, 24 hours, under Ar, isolated yields.





On the basis of the above studies and the precedent reports, plausible pathways for this reaction are shown in Fig. 6. Catalytically active rhodium species **A** first coordinates to the P atom of indole **1** in the presence of ^{t}BuOLi, which leads to the formation of complex **B**. A reversible cyclometalation through a ^{t}butoxide-assisted deprotonation at the indole C7 position delivers the intermediate **C** and further generates a rhodacycle **D**. Then, the oxidative addition of aryl halide **2** to intermediate **D** affords **E** species. Subsequent reductive elimination and dissociation (**F**) delivers C7 arylation product **3** and regenerates active catalyst **A** (pathway A). An alternative process involves oxidative addition of the Wilkinson's catalyst into aryl halide **2** (**I**)

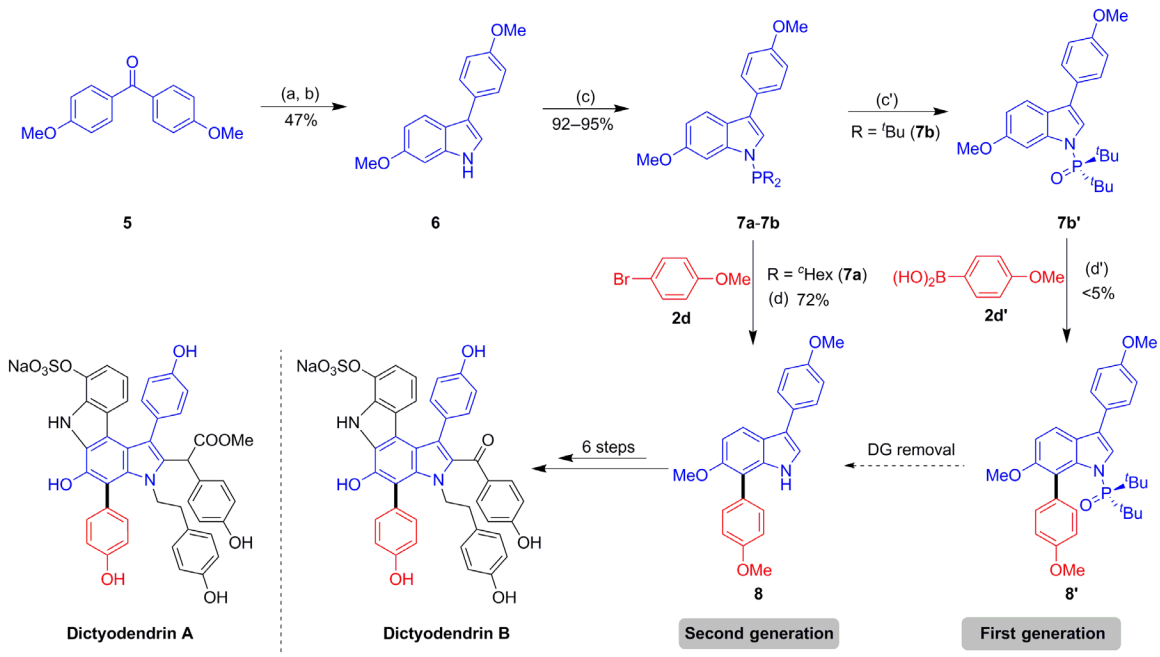


Fig. 3. Application as a key step in the synthesis of dictyodendrin B. Reaction conditions: (a) $MeNO_2$, LiHMDS, 51%; (b) $Pd(OAc)_2$ (2 mol %), Phen (4 mol %), CO (1 atm), DMF, 110°C, 93%; (c) $^tBu_2PCl$, or $^cHex_2PCl$, ^nBuLi, 92 to 95%; (c′) after procedure (c), then H_2O_2, 99%; (d) $Rh(PPh_3)_3Cl$ (10 mol %), LiO^tBu (3.0 equiv), **2d** (10.0 equiv), *m*-xylene, 160°C, then add dilute HCl, 10 min, 72%; (d′) $Pd(OAc)_2$ (10 mol %), 2-Cl-pyridine (20 mol %), $Cu(OTf)_2$ (0.5 equiv), Ag_2O (2.0 equiv), CuO (1.0 equiv), dioxane, 120°C, Ar, trace in gas chromatography–mass spectrometry.

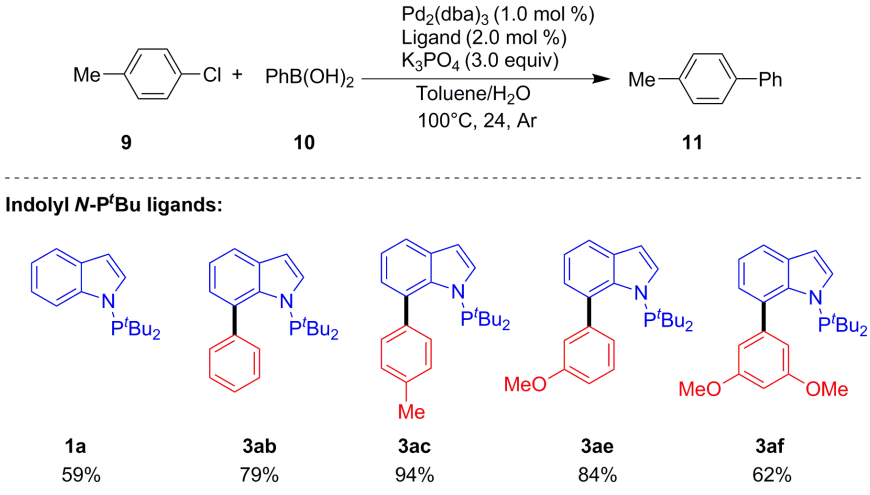


Fig. 4. Preliminary investigation of the developed ligands in Suzuki-Miyaura couplings of aryl chlorides. Reaction conditions: **11** (0.20 mmol), **12** (0.40 mmol), $Pd_2(dba)_3$ (1.0 mol%), ligand (2.0 mol%), and K_3PO_4 (3.0 equiv) in *m*-xylene (1.0 ml) and H_2O (1.0 ml) at 100°C, 24 hours, under Ar.

ahead of C–H activation, and then the base-assisted metalation of indole **1** (**II**) affording the same intermediate **E** cannot be ruled out at the current stage (pathway B) (*12*, *58*, *59*). Additional investigation is necessary to fully elucidate the details of the reaction mechanism.

CONCLUSION

In summary, we have reported an efficient C7-selective direct arylation of indoles with *N*-PR_2 (R = ^{t}Bu and ^{c}Hex) directing groups. This reaction, which uses the commercially available Wilkinson's catalyst, does not require the addition of an exogenous ligand, and it is applicable with a broad range of coupling partners including electron-rich, electron-poor, and sterically hindered (hetero)aryl bromides with a variety of indoles. This novel strategy has many advantages including the directing group being easier to access and remove, using cheaper and more widely available aryl bromides/chlorides as arylating agents, not requiring an external ligand or oxidant, having a broader substrate scope, being more efficient, and producing only one regioisomer. The practicality of this method was also demonstrated by the synthesis of a key intermediate in the synthesis of dictyodendrin B and the applications

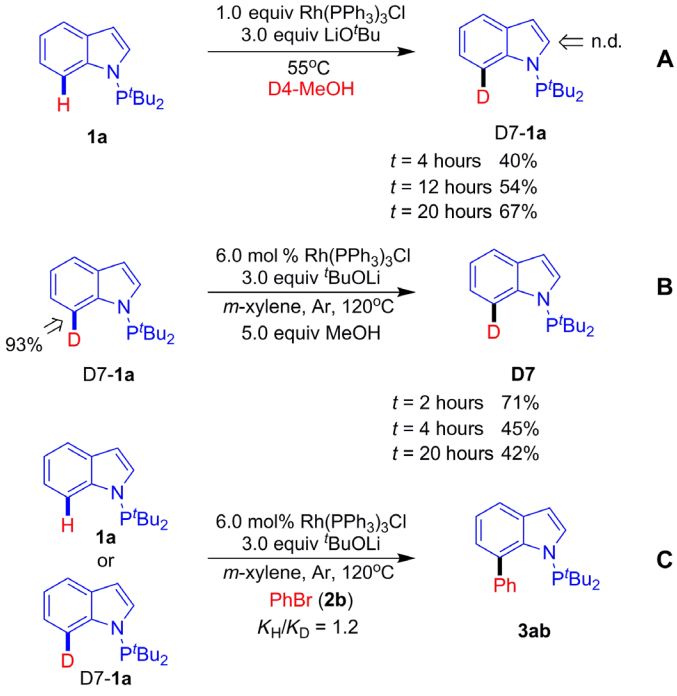


Fig. 5. Deuterium labeling experiments and the study of kinetic isotope effect. n.d., not detected.

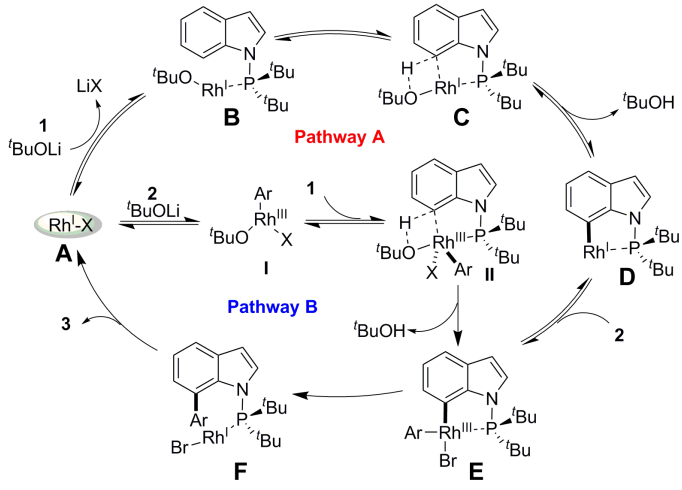


Fig. 6. Plausible reaction pathways.

as a class of potential indolyl phosphine ligands. These present results represent an important discovery that is expected to be substantially extended to other new transformations.

MATERIALS AND METHODS

General information

Unless otherwise noted, all reactions were performed under an argon atmosphere using a flame-dried glassware. Toluene, chlorobenzene, and *m*-xylene were distilled over CaH_2. All new compounds were fully characterized. NMR spectra were recorded on a Bruker AV-300, an ARX-400 MHz, or an ARX-600 Associated. ^{1}H NMR spectra data were reported as δ values in parts per million (ppm) relative to chloroform (δ = 7.26) if collected in $CDCl_3$. ^{13}C NMR spectra data were reported as δ values in ppm relative to chloroform (δ = 77.0) if collected in $CDCl_3$. Mass spectrometry was conducted with the Micromass Q-TOF Instrument (ESI) and Agilent Technologies 5973N (EI). All reactions were carried out in flame-dried 25-ml Schlenk tubes with Teflon screw caps under argon. $Rh(PPh_3)_3Cl$ and $[Rh(cod)Cl]_2$ were purchased from J&K. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.

General procedure for the synthesis of *N*-P^{t}Bu$_2$ indoles 1a to 1t

To a solution of indole (5.0 mmol, 1.0 equiv) in 10 ml of anhydrous tetrahydrofuran (THF) at 0°C, a solution of ^{n}BuLi (2.5 M solution in hexane, 2.4 ml, 1.2 equiv) was added dropwise. After stirring for 15 min, P^{t}Bu$_2$Cl (1.08 g, 1.2 equiv) was added dropwise. The mixture was allowed to stir and warm to room temperature over several hours. After indole was consumed as determined by thin-layer chromatography (TLC), the reaction was quenched by 2 ml of MeOH. Then, the solvent was removed under reduced pressure. Further purification was performed through flash chromatography [petroleum ether/ethyl acetate (PE/EA) = 50:1] to obtain the pure product.

General procedure for the synthesis of *N*-P^{c}Hex$_2$ indoles 1a′ to 1u′

To a solution of indole (5.0 mmol, 1.0 equiv) in 10 ml of anhydrous THF at 0°C, a solution of ^{n}BuLi (2.5 M solution in hexanes, 2.02 ml, 1.05 equiv) was added dropwise. After stirring for 30 min, P^{c}Hex$_2$Cl (1.17 g, 1.05 equiv) was added dropwise. The mixture was allowed to stir and warm to room temperature over several hours. After indole was consumed as determined by TLC, the solvent was removed by a vacuum. The crude products were purified by neutral alumina column chromatography with petroleum ether and ethyl acetate as eluent.

General procedure for *N*-P^{t}Bu$_2$ directed C7 arylation of indoles

To a 25-ml Schlenk tube, indole substrates **1** (0.20 mmol), aryl bromides **2** (0.30 to 0.4 mmol), $Rh(PPh_3)_3Cl$ (11.1 mg, 0.012 mmol), and LiO^{t}Bu (48.0 mg, 0.60 mmol) were added. The tube was purged with Ar three times, followed by the addition of anhydrous *m*-xylene (1.0 ml). The mixture was stirred at 80° to 150°C for 24 hours. The solution was then cooled to room temperature, and the solvent was removed under vacuum directly. The crude product was purified by column chromatography on silica gel and gave the pure products **3**.

General procedure for *N*-P^{c}Hex$_2$ directed C7 arylation of indoles

To a 25-ml Schlenk tube, indole substrates **1′** (0.20 mmol), aryl bromides **2** (0.4 mmol), $Rh(PPh_3)_3Cl$ (11.1 mg, 0.012 mmol), and LiO^{t}Bu (48.0 mg, 0.60 mmol) were added. The tube was purged with Ar three times, followed by the addition of anhydrous *m*-xylene (1.0 ml). The mixture was stirred at 150°C for 24 hours. The solution was cooled to room temperature and 0.5 ml of HCl (4.0 M in dioxane) was added, and then the solution was stirred in open air at room temperature for 10 min. After that, 0.4 ml of Et_3N was added, and the solvent was removed under vacuum directly. There was another way to work up the reaction: After the reaction was cooled to room

temperature, 0.5 g of silica gel was added, and the solvent was removed under vacuum directly. The crude product was purified by column chromatography on silica gel and gave the pure products **4**.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/4/12/eaau6468/DC1

Fig. S1. Test the indole *N*-PPh_2–directed C7 arylation reaction.
Fig. S2. General procedure for the investigation of the developed ligands in Suzuki-Miyaura coupling.
Fig. S3. Single-crystal x-ray structure determination of compound **3aa** (CCDC no. 1838725).
Table S1. Deuteration experiments with indole **1a**.
Table S2. Deuteration experiments with indole **D7-1a**.
Table S3. Study of kinetic isotope effect.
Data file S1. Characterization of isolated compounds.
Data file S2. X-ray crystal data of **3aa**.
Data file S3. ^{1}H, ^{13}C, ^{31}P, and ^{19}F NMR spectra.

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