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Pd-Catalyzed Alkene Carboheteroarylation Reactions for the Synthesis of 3-Cyclopentylindole Derivatives

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Abstract

The Pd-catalyzed alkene carboheteroarylation of aryl and alkenyl triflate electrophiles bearing pendant alkenes with heteroaromatic nucleophiles affords substituted carbocycles with 3-indolyl or 3-pyrrolyl groups. The products are obtained in moderate to good yield, and use of alkenyl triflate substrates produces products with high diastereoselectivity. The transformation is believed to proceed via a Friedel-Crafts-like reaction between the heteroaromatic nucleophile and an intermediate electrophilic palladium complex.

Graphical abstract

Over the past 14 years, our group has focused on the development of a number of new Pd-catalyzed alkene difunctionalization reactions.¹ Recently, we have described a new class of alkene difunctionalization reactions between aryl/alkenyl triflates (e.g., **1a**) bearing a tethered alkene, and exogenous amine, alcohol, or phenol nucleophiles.² These transformations afford products such as **2a–b** in high yield with high diastereoselectivity, and generate a carbon-carbon bond, a carbon-heteroatom bond, and a carbocyclic ring in one step (eq 1). To date, we have only described the use of heteroatom-centered nucleophiles in these reactions. In order to further explore the scope of this method, we sought to examine transformations of heteroaromatic nucleophiles, such as indole. These species are inherently less nucleophilic than amines or alkoxides/phenoxides, and have been shown to act as either C-nucleophiles or N-nucleophiles under appropriate conditions in Pd-catalyzed indole alkylation/arylation reactions.^{3,4} In this letter we describe the coupling of **1** with indole nucleophiles **3** to afford 3-cyclopentylindole derivatives **4** (eq 2).⁵

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Supporting Information

Descriptions of stereochemical assignments and copies of ¹H and ¹³C NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Notes

The authors declare no competing financial interests.

In preliminary studies, we examined the Pd/BrettPhos-catalyzed reaction of 2-allylphenyl triflate **1b** with 5-methoxyindole **3a**, using conditions that generally provided satisfactory results with amine and alcohol nucleophiles. This reaction afforded 25% of the C3-alkylated product **4a** as judged by ¹H NMR analysis of the crude reaction mixture (Table 1, entry 1). Other Buchwald-type biaryl phosphine ligands were screened and XPhos was found to give the best yield relative to conversion to product (entries 2–3). Increasing the temperature to 105 °C resulted in a slightly improved 40% yield (entry 4). Changing the counterion of the *tert*-butoxide base to Na or K, or changing the base to LiHMDS led to a decrease in yield due to the formation of a number of unidentified side products (entries 5–7). However, when the reaction concentration was increased to 1 M the desired product was generated in 62% yield (entry 8).

Despite some improvement during the initial optimization studies, the yields proved to be rather difficult to consistently reproduce. After some exploration, we observed that the highest yields were obtained when the solvent evaporated during the 16 hour reaction time. We reasoned that transformations of the weakly nucleophilic indoles might be improved by omitting the solvent; however, when the reactions were conducted with no solvent we obtained unsatisfactory results. It seemed the difference in the outcomes for these two sets of conditions (evaporation vs. neat) may be due to a need for solvent during the catalyst activation process.⁶ As such, we developed a protocol in which the reactions were conducted in benzene as the solvent (1 M) in a round bottom flask equipped with a short-path distillation head. After all reagents were mixed in the reaction vessel, the mixture was heated to 100 °C for 15–30 minutes while the benzene solvent was removed via distillation. The reaction temperature was then decreased to 95 °C while the reaction stirred for an additional three hours. This protocol provided consistent and reproducible results with a variety of substrates, and allowed us to decrease the reaction time significantly from ~16 h to ~3.5 h.

With the optimized conditions in hand, we examined the reactivity of 2-allylphenyl triflate **1b** or 1-allyl-2-naphthyl triflate **1c** with several different aromatic heterocycles (Scheme 1). The coupling of **1b** proceeded smoothly with indole, 2-methylindole, and 5-methoxyindole to afford **4a-c**, and **1b** and **1c** was coupled with 5-methoxy indole in good yield (**4e**).⁷ In the

synthesis of **4c**, use of 6 mol % XPhos provided comparable results to those obtained with 12 mol % XPhos on both our standard 0.5 mmol scale and a slightly larger 1 mmol scale. Use of 2,5-Dimethylpyrrole as the nucleophile produces the desired product **4d** in up to 80% yield as determined by ^1H NMR analysis of the crude reaction mixture. However, compound **4d** is rather air-sensitive, and a low isolated yield of 35% was obtained due to partial oxidation/decomposition during purification. Additionally, a second product was observed in low yields that, based on GC/MS and ^1H NMR analysis, we have tentatively assigned as an over-alkylated 2,5-dimethylpyrrole derivative bearing 2-indanyl groups at both the C3 and C4 positions. Efforts to employ N-alkyl indoles, benzofuran, or benzothiophene as the nucleophile failed to provide the desired products. This suggests the substrate N-H proton is required to achieve the desired reactivity, and may be removed prior to the reaction of the indole with the intermediate palladium complex **8** (see below in Scheme 3).

Given that the Pd-catalyzed C3 alkylation of 3-alkylindole derivatives to afford products bearing a quaternary carbon center is well-established,⁸ we examined the coupling of **1b** with 3-methylindole. Our optimized conditions led to no reaction, but when the mixture was heated to 150 °C, the formation of *N*-alkylindole product **5** was observed, albeit in low yield (eq 3). While attempting to further optimize this reaction, we found that use of CPhos as ligand and LiHMDS as base produced a mixture of **5** along with an unexpected 5-exo cyclization/C3-alkylation product **6** (eq 4).^{9,10} Further efforts to optimize the selectivity and yields of either **5** or **6** have thus far been unsuccessful.

We also examined the effect of substitution along the allyl group on reactivity, and found the transformations are quite sensitive to substrate steric properties. A 2-allylphenyltriflate derivative bearing a methyl group at the internal alkene carbon atom (**1d**) proved to be unreactive (eq 5). In contrast, substrate **1e** that contains an allylic methyl group was transformed to **4f** in 30% NMR yield with good diastereoselectivity (eq 6).¹¹ However, compound **4f** proved to be inseparable from unreacted indole, and a 1:1 mixture of **4f**:indole was obtained in low yield after chromatography (ca 13% of **4f** was obtained based on the mixture).

Since our prior studies have shown that both aryl and alkenyl triflate electrophiles can be coupled with alcohol or amine nucleophiles (e.g., eq 1, **1a** $\rightarrow$ **2a-b**),^{2b-c} we explored the use of alkenyl triflate electrophiles **1a** and **1f-h** in reactions with indoles (Scheme 2). We were pleased to find that these electrophiles were successfully coupled with indole and 6-chloroindole to afford **4g-h** in good yields with high diastereoselectivity (entries 1–2).

Although the presence of a methyl group at the allylic position of aryl triflate **1e** was not well tolerated, substrate **1f**, which contains a methyl group at the homoallylic position, was coupled with indole in 50% yield (**4i**, >20:1 dr). In addition, substrates **1g-h** that contain heteroatoms in their backbones were transformed to products **4j-k** in low to moderate yields with good (10 to >20:1) diastereoselectivities. Given the hazards associated with the use of benzene, we also briefly examined alternative solvents for these transformations. Use of 2-methyl THF in the coupling of **1a** with indole afforded the desired product **4g** in 64% yield, which is comparable to the 73% yield obtained with benzene. In contrast, use of toluene as solvent required a higher temperature for the distillation step (130 $^\circ\text{C}$), and the desired product was obtained in 48% yield.

Our current mechanistic hypothesis for this transformation is illustrated in Scheme 3, and is similar to that for reactions involving amine or alcohol nucleophiles.² The catalytic cycle is initiated by reduction of the Pd(II) precatalyst to Pd(0), followed by oxidative addition of the triflate electrophile (e.g., **1b**) to afford cationic Pd(II) species **7**. Coordination of the alkene to the Pd-center affords **8**, in which the alkene is rendered electrophilic at the internal alkene carbon. A sequence involving deprotonation of the indole followed by a Friedel-Crafts-like *anti*-carbopalladation gives the 6-membered palladacycle **9**, which is converted to **10** upon tautomerization of the 3*H* indole to a 1*H* indole.¹² Reductive elimination from **10** leads to formation of the second C–C bond to afford the product (**4c**) with concomitant regeneration of the active Pd(0) catalyst.

In conclusion, we have developed a new Pd-catalyzed alkene difunctionalization reaction that effects intramolecular arylation and intermolecular heteroarylation of the alkene. This reaction forms two carbon-carbon bonds in one step to afford 3-cyclopentylindole derivatives in good yield and high diastereoselectivity. Future studies will be directed towards the use of other carbon-centered nucleophiles in these types of transformations.

Experimental Section

General: All reactions were carried out under a nitrogen atmosphere using oven or flame-dried glassware. All palladium sources and reagents were obtained from commercial sources and used without further purification unless otherwise noted. Aryl and alkenyl triflate substrates **1a**,^{2b} **1b-c**,^{2a} **1d-e**,^{2c} and **1f-h**^{2b} were prepared according to previously reported procedures. Toluene was purified using a GlassContour solvent system. Benzene was purified by distillation from calcium hydride under a nitrogen atmosphere. 2,5-Dimethylpyrrole was distilled from calcium hydride under a nitrogen atmosphere and stored in a re-sealable Schlenk tube in the glove box. Anhydrous 2-Methyltetrahydrofuran was obtained from commercial sources and was used without further purification. All yields refer to isolated compounds that are estimated to be 95% pure as judged by ¹H NMR analysis unless otherwise noted. *The yields reported in the experimental section describe the result of a single experiment, whereas yields reported in Schemes 1–2 and equations 3–4 are average yields of two or more experiments. Thus, the yields reported in the experimental section may differ from those shown in Schemes 1–2 and equations 3–4.*

Synthesis and Characterization of Products

General Procedure for Pd-Catalyzed Alkene Difunctionalization Reactions.—A flame-dried round bottom flask equipped with a stirbar was cooled under a stream of N₂ and charged with Pd(OAc)₂ (4 mol %), XPhos (12 mol %), the appropriate nucleophile (0.6 mmol, 1.2 equiv), and lithium *tert*-butoxide (0.7 mmol, 1.4 equiv). The tube was purged with N₂ and a solution of the appropriate aryl or alkenyl triflate (0.5 mmol, 1.0 equiv) in benzene (0.5 mL, 1M) was added. A short path distillation apparatus was attached to the flask, and the mixture was heated to 100–105 °C until the benzene had been removed by distillation. The reaction temperature was decreased to 95 °C and stirring was continued for 3 h. The mixture was cooled to rt, satd. NH₄Cl (aq) (2 mL) was added and the mixture was transferred to a separatory funnel. The layers were separated, the aqueous layer was extracted with EtOAc (3 mL x 2), then the organic layers were combined, dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

3-(2,3-Dihydro-1H-inden-2-yl)-5-methoxy-1H-indole (4a).—The general procedure was used for the coupling of 5-methoxyindole (88.3 mg, 0.6 mmol) and **1b** (133.1 mg, 0.5 mmol). The crude product was purified by flash chromatography on silica gel (100% DCM) to afford 89.1 mg (68%) of the title compound as a light pink oil. ¹H NMR (500 MHz, CDCl₃) δ 7.80 (s, 1 H), 7.30–7.24 (m, 3 H), 7.21–7.16 (m, 2 H), 7.02 (dd, *J* = 18.2, 2.4 Hz, 2 H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1 H), 3.91 (pent, *J* = 8.2 Hz, 1 H), 3.83 (s, 3 H), 3.43 (dd, *J* = 15.4, 8.0 Hz, 2 H), 3.16 (dd, *J* = 15.4, 8.3 Hz, 2 H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 153.9, 143.6, 132.0, 127.5, 126.4, 124.6, 121.2, 120.3, 112.2, 112.0, 101.7, 56.1, 40.0, 37.1. IR (film) 3414, 2935, 2831, 1623, 1581, 1481 cm⁻¹; HRMS (ESI⁺ TOF) *m/z*: [M + H]⁺ Calcd for C₁₈H₁₈NO 264.1383; Found 264.1385.

3-(2,3-Dihydro-1H-inden-2-yl)-2-methyl-1H-indole (4b).—The general procedure was used for the coupling of 2-methylindole (78.7 mg, 0.6 mmol) and **1b** (133.1 mg, 0.5 mmol).

The crude product was purified by flash chromatography on silica gel (100% DCM) to afford 79.7 mg (64%) of the title compound as a white solid, m.p. 158–159 °C). ¹H NMR (500 MHz, CDCl₃) δ 7.72 (s, 1 H), 7.44 (d, *J* = 7.9 Hz, 1 H), 7.32–7.24 (m, 3 H), 7.24–7.19 (m, 2 H), 7.13–7.07 (m, 1 H), 7.02–6.95 (m, 1 H), 3.89 (p, *J* = 9.3 Hz, 1 H), 3.45 (dd, *J* = 15.9, 9.8 Hz, 2 H), 3.22 (dd, *J* = 15.9, 8.8 Hz, 2 H), 2.42 (s, 3 H). ¹³C{¹H} (126 MHz, CDCl₃) δ 143.9, 135.7, 130.7, 127.4, 126.4, 124.6, 121.0, 119.5, 119.0, 114.5, 110.5, 39.7, 36.7, 12.3. IR (film) 3391, 2932, 2844 cm⁻¹; HRMS (ESI⁺ TOF) *m/z*: [M + H]⁺ Calcd for C₁₈H₁₈N 248.1434; Found 248.1430.

3-(2,3-Dihydro-1*H*-inden-2-yl)-1*H*-indole (4c).—The general procedure was used for the coupling of indole (70.3 mg, 0.6 mmol) and **1b** (133.1 mg, 0.5 mmol). The crude product was purified by flash chromatography on silica gel (5% hexanes in DCM) to afford 89.0 mg (76%) of the title compound as a pale yellow solid, m.p. 80–83 °C). ¹H NMR (500 MHz, CDCl₃) δ 7.91 (s, 1 H), 7.66 (d, *J* = 7.9 Hz, 1 H), 7.38 (d, *J* = 8.1 Hz, 1 H), 7.30–7.24 (m, 2 H), 7.24–7.14 (m, 3 H), 7.12 (app t, *J* = 7.2 Hz, 1 H), 7.02 (d, *J* = 1.6 Hz, 1 H), 3.96 (pent, *J* = 8.3 Hz, 1 H), 3.43 (dd, *J* = 15.3, 8.0 Hz, 2 H), 3.19 (dd, *J* = 15.3, 8.6 Hz, 2 H). ¹³C{¹H} (126 MHz, CDCl₃) δ 143.5, 136.8, 127.1, 126.4, 124.6, 122.2, 120.4, 120.3, 119.6, 119.4, 111.3, 40.1, 37.1. IR (film) 3416, 3046, 2976, 2842, 1456 cm⁻¹; HRMS (ESI⁺ TOF) *m/z*: [M + H]⁺ Calcd for 234.1277 C₁₇H₁₆N; Found 234.1275.

3-(2,3-Dihydro-1*H*-inden-2-yl)-1*H*-indole (4c).—The general procedure was used for the coupling of indole (70.3 mg, 0.6 mmol) and **1b** (133.1 mg, 0.5 mmol) except using 6 mol % of XPhos (14.3 mg, 0.03 mmol) rather than 12 mol %. The crude product was purified by flash chromatography on silica gel (5% hexanes in DCM) to afford 81.2 mg (70%) of the title compound as a pale yellow solid, m.p. 80–83 °C). Spectroscopic data were identical to those reported above.

3-(2,3-Dihydro-1*H*-inden-2-yl)-1*H*-indole (4c).—The general procedure was used for the coupling of indole (140.6 mg, 1.2 mmol) and **1b** (266.2 mg, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (5% hexanes in DCM) to afford 143.1 mg (61%) of the title compound as a pale yellow solid, m.p. 80–83 °C). Spectroscopic data were identical to those reported above.

3-(2,3-Dihydro-1*H*-inden-2-yl)-2,5-dimethyl-1*H*-pyrrole (4d).—A flame-dried Schlenk tube equipped with a stirbar was cooled under a stream of N₂ and charged with Pd(OAc)₂ (0.0045g, 4 mol %), BrettPhos (0.0268g, 10 mol %), and lithium *tert*-butoxide (0.0560g, 0.7 mmol). The tube was purged with N₂ (g) and 4.5 mL of toluene and a solution of **1b** (133.1 mg, 0.5 mmol) in toluene (0.5 mL) was added. 2,5-Dimethylpyrrole (61 μL, 0.6 mmol) was added directly to the reaction mixture via syringe, then the reaction mixture was heated to 95 °C with stirring for 16 h. The mixture was then cooled to rt, satd. NH₄Cl (aq) (5 mL) was added, the mixture was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 mL x 2), then the organic layers were combined, dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford 41.0 mg (39%) of the title compound as a yellow solid, m.p. 91–94 °C.

¹H NMR (500 MHz, CDCl₃) δ 7.41 (s, 1 H), 7.25–7.17 (m, 2 H), 7.17–7.10 (m, 2 H), 5.72 (d, *J* = 2.8 Hz, 1 H), 3.52 (tt, *J* = 9.6, 8.0 Hz, 1 H), 3.16 (dd, *J* = 15.3, 7.9 Hz, 2 H), 2.95 (dd, *J* = 15.3, 9.6 Hz, 2 H), 2.20 (s, 6 H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 143.9, 126.2, 125.2, 124.3, 122.7, 121.9, 104.4, 41.2, 37.7, 13.1, 11.3. IR (film) 3331, 2896, 2839 cm⁻¹; HRMS (ESI⁺ TOF) *m/z*: [M + H]⁺ Calcd for C₁₅H₁₈N 212.1434; Found 212.1432.

3-(2,3-Dihydro-1*H*-cyclopenta[*a*]naphthalen-2-yl)-5-methoxy-1*H*-indole (4e).—

The general procedure was used for the coupling of 5-methoxyindole (88.3 mg, 0.6 mmol) and **1c** (158.1 mg, 0.5 mmol) except using 6 mol % of XPhos (14.3 mg, 0.03 mmol) rather than 12 mol %. The crude product was purified by flash chromatography on silica gel (100% DCM) to afford 106.2 mg (68%) of the title compound as a white foam. ¹H NMR (500 MHz, CDCl₃) δ 7.87 (dd, *J* = 7.8, 1.3 Hz, 1 H), 7.84–7.76 (m, 2 H), 7.73 (d, *J* = 8.3 Hz, 1 H), 7.49 (ddd, *J* = 8.3, 6.8, 1.5 Hz, 1 H), 7.43 (dd, *J* = 8.2, 6.3 Hz, 2 H), 7.24 (d, *J* = 3.3 Hz, 1 H), 7.02 (dd, *J* = 3.7, 2.4 Hz, 2 H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1 H), 4.16–4.04 (m, 1 H), 3.81 (dd, *J* = 15.8, 8.4 Hz, 1 H), 3.75 (s, 3 H), 3.62 (dd, *J* = 15.7, 8.4 Hz, 1 H), 3.46 (dd, *J* = 15.8, 7.4 Hz, 1 H), 3.35 (dd, *J* = 15.8, 7.4 Hz, 1 H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 153.9, 140.4, 138.8, 132.8, 132.0, 130.6, 128.6, 127.4, 127.1, 126.1, 124.9, 124.4, 123.5, 121.2, 120.8, 112.2, 112.0, 101.7, 56.0, 41.1, 38.4, 36.5. IR (film) 3420, 3052, 2930, 2832, 1625, 1582 cm⁻¹; HRMS (ESI⁺ TOF) *m/z*: [M + H]⁺ Calcd for C₂₂H₂₀NO 314.1539; Found 314.1537.

3-(1-Methyl-2,3-dihydro-1*H*-inden-2-yl)-1*H*-indole (4f).—The general procedure was used for the coupling indole (70.3 mg, 0.6 mmol) and **1e** (140.1 mg, 0.5 mmol) except using 6 mol % of XPhos (14.3 mg, 0.03 mmol) rather than 12 mol %. The crude product was purified by flash chromatography on silica gel (3% EtOAc in hexanes) to afford 38.2 mg as an inseparable mixture of the title compound and indole as a yellow oil. Of this mixture, ca. 16.0 mg (13%) was the title compound, based on ¹H NMR analysis of the mixture. The title compound was obtained as a ca 10:1 mixture of diastereomers. The relative stereochemistry of the major isomer has tentatively been assigned as *trans* based on the outcome of a prior reaction of this substrate with a phenol nucleophile,^{2c} but efforts to unambiguously assign stereochemistry by nOe have been unsuccessful. ¹H NMR (500 MHz, CDCl₃) δ 7.95 (s, 1 H), 7.69–7.64 (m, 1 H), 7.46–7.38 (m, 1 H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.27–7.19 (m, 3 H), 7.17–7.05 (m, 3 H), 3.57–3.44 (m, 1 H), 3.43–3.32 (m, 2 H), 3.27–3.17 (m, 1 H), 1.39 (d, *J* = 6.8 Hz, 3 H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 148.1, 143.0, 136.9, 127.3, 126.5, 124.4, 123.3, 122.2, 120.9, 120.0, 119.3, 118.8, 111.4, 46.8, 45.8, 39.7, 18.3. IR (film) 3415, 3056, 2956 cm⁻¹; HRMS (ESI⁺ TOF) *m/z*: [M + H]⁺ Calcd for C₁₈H₁₈N 248.1434; Found 248.1432.

3-(2,3,3a,4,5,6-Hexahydro-1*H*-inden-2-yl)-1*H*-indole (4g).—The general procedure was used for the coupling of indole (70.3 mg, 0.6 mmol) and **1a** (135.1 mg, 0.5 mmol) except 6 mol % of XPhos (14.3 mg, 0.03 mmol) was used instead of 12 mol %. The crude product was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford 87.4 mg (74%, >20:1 dr) of the title compound as a yellow solid, m.p. 91–93 °C). ¹H NMR (500 MHz, C₆D₆) δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.28 – 7.17 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.54 (s, 1H), 6.48 – 6.45 (m, 1H), 5.49 – 5.43 (m, 1H), 3.43 – 3.20 (m, 1H), 3.04 – 2.89 (m,

1H), 2.57 – 2.44 (m, 1H), 2.33 – 2.19 (m, 2H), 2.10 – 2.01 (m, 2H), 2.00 – 1.92 (m, 1H), 1.83 – 1.67 (m, 1H), 1.57 – 1.34 (m, 2H), 1.20 – 1.00 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, C_6D_6) δ 144.3, 137.3, 122.2, 120.9, 120.1, 119.7, 119.4, 117.8, 111.4, 42.2, 41.5, 38.2, 35.0, 29.4, 25.8, 23.1, one carbon signal is missing due to accidental equivalence. IR (film) 3414, 3055, 2920, 2852 cm^{-1} ; HRMS (ESI⁺ TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{20}\text{N}$ 238.1596; Found 238.1592.

3-(2,3,3a,4,5,6-Hexahydro-1H-inden-2-yl)-1H-indole (4g).—The general procedure was used for the coupling of indole (70.3 mg, 0.6 mmol) and **1a** (135.1 mg, 0.5 mmol) except 6 mol % of XPhos (14.3 mg, 0.03 mmol) was used instead of 12 mol %, and the reaction was carried out in 2-methyl THF solvent with an initial temperature of 110 °C. The crude product was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford 76.7 mg (64%, >20:1 dr) of the title compound as a yellow solid, m.p. 91–93 °C). Spectroscopic data were identical to those reported above.

3-(2,3,3a,4,5,6-Hexahydro-1H-inden-2-yl)-1H-indole (4g).—The general procedure was used for the coupling of indole (70.3 mg, 0.6 mmol) and **1a** (135.1 mg, 0.5 mmol) except 6 mol % of XPhos (14.3 mg, 0.03 mmol) was used instead of 12 mol %, and the reaction was carried out in toluene solvent with an initial temperature of 130 °C. The crude product was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford 57.2 mg (48%, >20:1 dr) of the title compound as a yellow solid, m.p. 91–93 °C). Spectroscopic data were identical to those reported above.

6-Chloro-3-(2,3,3a,4,5,6-hexahydro-1H-inden-2-yl)-1H-indole (4h).—The general procedure was used for the coupling of 6-chlorolindole (91.0 mg, 0.6 mmol) and **1a** (135.1 mg, 0.5 mmol) except 6 mol% of XPhos (14.3 mg, 0.03 mmol) was used instead of 12 mol %. The crude product was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford 81.9 mg (60%, >20:1 dr) of the title compound as a yellow solid, m.p. 86–90 °C). ^1H NMR (400 MHz, C_6D_6) δ 7.40 (d, J = 8.5 Hz, 1H), 7.21 – 7.12 (m, 2H), 7.07 (d, J = 1.9 Hz, 1H), 6.35 (s, 1H), 5.47 (s, 1H), 3.28 – 3.07 (m, 1H), 2.89 (dd, J = 16.7, 10.1 Hz, 1H), 2.43 – 2.32 (m, 1H), 2.32 – 2.12 (m, 2H), 2.12 – 2.00 (m, 2H), 1.99 – 1.90 (m, 1H), 1.84 – 1.70 (m, 1H), 1.58 – 1.41 (m, 1H), 1.32 (q, J = 11.4 Hz, 1H), 1.18 – 1.02 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, C_6D_6) δ 144.0, 137.4, 126.3, 121.0, 120.9, 120.4, 120.0, 118.0, 111.4, 42.1, 41.3, 38.0, 34.7, 29.3, 25.8, 23.0, one carbon signal is missing due to accidental equivalence. IR (film) 3424, 2920, 2852 cm^{-1} ; HRMS (ESI⁺ TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{19}\text{ClN}$ 272.1201; Found 272.1191.

3-(3a-Methyl-2,3,3a,4,5,6-hexahydro-1H-inden-2-yl)-1H-indole (4i).—The general procedure was used for the coupling of indole (70.3 mg, 0.6 mmol) and **1f** (142.1 mg, 0.5 mmol) except 6 mol% of XPhos (14.3 mg, 0.03 mmol) was used instead of 12 mol %. The crude product was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford 63.1 mg (50%, >20:1 dr) of the title compound as a pale yellow solid, m.p. 84–87 °C). ^1H NMR (500 MHz, CDCl_3) δ 7.86 (s, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.35 (dd, J = 8.2, 1.0 Hz, 1H), 7.18 (ddd, J = 8.2, 7.0, 1.3 Hz, 1H), 7.09 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 6.97 (d, J = 2.2 Hz, 1H), 5.37 (s, 1H), 3.94 – 3.52 (m, 1H), 3.16 – 2.96 (m, 1H), 2.53 – 2.31 (m, 1H),

2.12 (dd, $J = 11.9, 7.0$ Hz, 1H), 2.08 – 1.98 (m, 2H), 1.86 – 1.78 (m, 1H), 1.73 – 1.67 (m, 2H), 1.62 (t, $J = 11.6$ Hz, 1H), 1.38 – 1.28 (m, 1H), 1.16 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 147.2, 137.0, 127.1, 122.0, 121.9, 119.9, 119.8, 119.1, 117.4, 111.3, 49.4, 41.5, 37.3, 36.5, 31.8, 25.5, 24.6, 19.1. IR (film) 3392, 2965, 2928, 2868, 2838, 1455 cm^{-1} ; HRMS (ESI⁺ TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{22}\text{N}$ 252.1747; Found 252.1749.

***tert*-Butyl 6-(5-methoxy-1*H*-indol-3-yl)-1,3,5,6,7,7a-hexahydro-2*H*-cyclopenta[*c*]pyridine-2-carboxylate (4j).**—The general procedure was used for the coupling of 5-methoxyindole (88.3 mg, 0.6 mmol) and **1g** (185.7 mg, 0.5 mmol) except 6 mol% of XPhos (14.3 mg, 0.03 mmol) was used instead of 12 mol %.

The crude product was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford 61.1 mg (33%, >20:1 dr) of the title compound as a yellow foam. ^1H NMR (500 MHz, Toluene- d_8) δ 7.28 (s, 1 H), 7.05–6.93 (m, 3 H), 6.52 (s, 1 H), 5.16 (s, 1 H), 4.79–4.07 (m, 2 H), 3.60 (s, 3 H), 3.52–3.42 (m, 1 H), 3.22 (s, 1 H), 2.90–2.71 (m, 1 H), 2.44 (s, 1 H), 2.38–2.20 (m, 2 H), 2.08–2.01 (m, 1 H), 1.50 (s, 9H), 1.26–1.14 (m, 1 H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, Toluene- d_8) δ 154.8, 144.4, 143.6, 132.9, 121.0, 120.9, 120.0, 115.6, 114.9, 112.7, 112.5, 102.4, 79.5, 55.8, 47.6–46.1 (m), 44.5–43.8 (m), 41.8, 41.6, 38.0, 37.9, 35.7, 29.0, the observed complexity is due to rotamers. IR (film) 3326, 2930, 2857, 1695, 1669 cm^{-1} ; HRMS (ESI⁺ TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{22}\text{H}_{29}\text{N}_2\text{O}_3$ 369.2173; Found 369.2175.

3-(1,3,5,6,7,7a-Hexahydrocyclopenta[*c*]pyran-6-yl)-1*H*-indole (4k).—The general procedure was used for the coupling of indole (70.3 mg, 0.6 mmol) and **1h** (136.1 mg, 0.5 mmol). The crude product was purified by flash chromatography on silica gel (10% EtOAc in hexanes) to afford 69.5 mg (58%, 10:1 dr) of the title compound as a yellow solid, m.p. 176–179 °C). ^1H NMR (500 MHz, C_6D_6) δ 7.65 (d, $J = 7.8$ Hz, 1H), 7.28 – 7.18 (m, 2H), 7.07 (d, $J = 8.0$ Hz, 1H), 6.56 (s, 1H), 6.41 (s, 1H), 5.22 (s, 1H), 4.30 – 4.13 (m, 2H), 4.07 – 3.96 (m, 1H), 3.32 – 3.18 (m, 1H), 3.06 (t, $J = 10.0$ Hz, 1H), 2.96 – 2.79 (m, 1H), 2.71 – 2.59 (m, 1H), 2.50 – 2.32 (m, 1H), 2.11 – 1.83 (m, 1H), 1.21 (q, $J = 11.7$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, C_6D_6) δ 142.3, 137.2, 127.9, 122.3, 120.3, 120.1, 119.7, 119.5, 117.1, 111.5, 69.6, 65.4, 41.1, 37.6, 36.6, 34.9. IR (film) 3253, 2966, 2924, 2856, 2744, 2718, 2709, 2702 cm^{-1} ; HRMS (ESI⁺ TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{18}\text{NO}$ 240.1383; Found 240.1383.

3-(2,3-Dihydro-1*H*-inden-2-yl)-5-methoxy-1*H*-indole (5).—The general procedure was used for the coupling of 3-methylindole (78.7 mg, 0.6 mmol) and **1b** (133.1 mg, 0.5 mmol) except 6 mol% of XPhos (14.3 mg, 0.03 mmol) was used instead of 12 mol %, and the reaction was stirred at 150 °C for 3 h rather than 95 °C. The crude product was purified by flash chromatography on silica gel (10% DCM in hexanes) to afford 26.0 mg (21%) of the title compound as a light pink oil. This material was judged to be ca 85% pure by ^1H NMR analysis. ^1H NMR (500 MHz, CDCl_3) δ 7.60 (d, $J = 7.8$ Hz, 1 H), 7.39 (d, $J = 8.3$ Hz, 1 H), 7.34–7.22 (m, 5 H), 7.18–7.12 (m, 1 H), 6.86 (d, $J = 1.3$ Hz, 1 H), 5.39–5.21 (m, 1 H), 3.54 (dd, $J = 16.2, 7.8$ Hz, 2 H), 3.32 (dd, $J = 16.2, 5.7$ Hz, 2 H), 2.31 (s, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 141.0, 136.2, 129.0, 127.1, 124.8, 122.5, 121.5, 119.2, 118.9, 110.7, 109.5, 55.7, 40.0, 9.8. IR (film) 3044, 2917, 2853 cm^{-1} ; HRMS (ESI⁺ TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{18}\text{N}$ 248.1434; Found 248.1434.

3-(Bicyclo[4.2.0]octa-1,3,5,7-tetra-7-ylmethyl)-3-methyl-3H-indole (6).—The general procedure was used for the coupling of 3-methylindole (78.7 mg, 0.6 mmol) and **1b** (133.1 mg, 0.5 mmol) except using 6 mol% of CPhos (13.1 mg, 0.03 mmol) as ligand, LiHMDS (0.1171 g, 0.7 mmol) as base, and the reaction was stirred at 150 °C for 3 h instead of 95 °C. The crude product was purified by flash chromatography on silica gel (10% DCM in hexanes then 20% EtOAc in hexanes) to afford 23.3 mg (19%, 85% purity) of **5** and 32.7 mg (26%, >20:1 dr) of the title compound as an orange oil. Data for **5** are provided above, and data for **6** are as follows. Although **6** was generated with high diastereoselectivity, we have been unable to establish the relative stereochemistry. ¹H NMR (500 MHz, CDCl₃) δ 8.08 (s, 1 H), 7.66 (d, *J* = 7.7 Hz, 1 H), 7.40–7.32 (m, 2 H), 7.30–7.23 (m, 1 H), 7.18–7.02 (m, 4 H), 3.10 (dd, *J* = 15.4, 8.2 Hz, 1 H), 2.99 (ddd, *J* = 17.7, 9.6, 8.2 Hz, 1 H), 2.81–2.67 (m, 2 H), 2.44 (dd, *J* = 15.9, 9.6 Hz, 1 H), 1.47 (s, 3 H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 178.1, 155.0, 143.2, 142.5, 142.2, 128.1, 126.6, 126.5, 126.5, 124.5, 124.5, 122.3, 121.4, 59.2, 45.4, 35.5, 35.2, 19.3. IR (film) 3021, 2934, 2245 cm⁻¹; HRMS (ESI⁺ TOF) *m/z*: [M + H]⁺ Calcd for C₁₈H₁₈N 248.1434; Found 248.1434.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- (6). When reactions were carried out in the absence of solvent, very little liquid is present in the reaction mixture (typically only the aryl/alkenyl triflate substrate). As such, in the absence of solvent it is possible that catalyst activation is inefficient simply due to the poor solubility of the precatalyst and ligand. Under the neat reaction conditions it appears that decomposition of the precatalyst (precipitation of unligated Pd) may occur at rates that are comparable to or greater than ligation and catalyst activation.
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- (10). We have been unable to establish the relative stereochemistry of 6. Efforts to convert 6 to a bicyclic derivative through Friedel-Crafts cyclization for use in nOe experiments instead lead to products resulting from carbocation rearrangements.
- (11). The stereochemistry of 4f has been tentatively assigned as trans based on analogy to the previously reaction of 1e with 4-methoxyphenol; see reference 2c. Efforts to assign the stereochemistry through 1H NMR nOe experiments provided ambiguous data.
- (12). It is also possible the tautomerization of the 3H indole to the 1H indole occurs after reductive elimination.

^aConditions: 1.0 equiv **1**, 1.2 equiv nucleophile, 4 mol % Pd(OAc)₂, 12 mol % XPhos, 1.4 equiv LiO^tBu, benzene (1 M), 100 °C to 95 °C, 3 h. ^bYields are isolated yields (average of two or more runs). ^cThe reaction was conducted with 6 mol % XPhos. ^dThe reaction was conducted with 10 mol % BrettPhos in toluene solvent (0.1 M) with a 16 h reaction time. ^eThe reaction was conducted on a 1 mmol scale with 6 mol % XPhos.

Scheme 1.
Reactions of Aryl Triflates^{a,b}

^aConditions: 1.0 equiv **1**, 1.2 equiv nucleophile, 4 mol % Pd(OAc)₂, 6 mol % XPhos, 1.4 equiv LiOtBu, benzene (1 M), 100 °C to 95 °C, 3 h. ^bYields are isolated yields (average of two or more runs). ^cThe reaction was conducted using 2-methyl THF in place of benzene as solvent, with an initial temperature of 110 °C. ^dThe reaction was conducted using toluene in place of benzene as solvent, with an initial temperature of 130 °C.

Scheme 2.
 Reactions of Alkenyl Triflates^{a,b}

Scheme 3.
Proposed Catalytic Cycle

Table 1.

Optimization Studies^a

Entry	Ligand	Base	Conversion (%)	Yield (%) ^b
1	BrettPhos	LiO ^t Bu	75	25
2	RuPhos	LiO ^t Bu	75	Trace
3	XPhos	LiO ^t Bu	25	25
4	XPhos	LiO ^t Bu	85	40 ^c
5	XPhos	NaO ^t Bu	>95	<50 ^{c,d}
6	XPhos	KO ^t Bu	>95	0 ^e
7	XPhos	LiHMDS	65	5 ^e
8	XPhos	LiO ^t Bu	>95	62 ^e

^aConditions: 1.0 equiv **1b**, 1.2 equiv **3a**, 4 mol % Pd(OAc)₂, 10 mol % ligand, 1.4 equiv base, toluene (0.1 M), 95 °C, 16 h. ^bYields were determined by ¹H NMR analysis using phenanthrene as an internal standard. ^cThe reaction was conducted at 105 °C. ^dThis material contains ca 30% of an unidentified side product. ^eThe reaction was conducted at 1 M concentration.