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Facile Assembly of Carbazolyl-Derived Phosphine Ligands and Their Applications in Palladium-Catalyzed Sterically Hindered Arylation Processes

Man Pan Leung, Pui Ying Choy, Wing In Lai, Kin Boon Gan, and Fuk Yee Kwong*

Department of Chemistry, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong

Supporting Information

ABSTRACT: Phosphine ligands embodying a carbazolyl motif have been found to be successful in many palladium-catalyzed biaryl syntheses and direct C−H bond arylation processes. Here, a practical scaled-up synthesis of a series of carbazolyl-derived phosphine ligands, the PhenCarPhos series, is described. The original protocol for accessing the target ligand skeleton via aromatic C−N bond formation is limited by the use of a substoichiometric amount of copper salt and diamine catalysts, which both add cost and generate purification problems (significant amounts of side products and copper residues). In order to develop a more attractive and scalable synthetic pathway, a simple nucleophilic substitution method was attempted involving simple heating of 1-bromo-2-fluorobenzene, a carbazole derivative, and KOH in DMF without inert atmosphere protection. This route enables the large-scale synthesis of the desired ligand skeletons and minimizes the association of inseparable reduction side products. Particular examples of the use of these ligands in Pd-catalyzed sterically hindered arylation processes are also shown.

KEYWORDS: *phosphine, arylation, palladium, sterically hindered, cross-coupling*

INTRODUCTION

Cross-coupling reactions are highly useful synthetic procedures for versatile carbon−carbon and carbon−heteroatom bond formations.[1] In the past decades, significant improvements of this modular transformation were mainly focused on the development of novel ancillary ligands. The steric and electronic properties of the phosphorus donor ligands have been documented to significantly impact the efficiency of Pd-catalyzed cross-coupling processes.[2] Our research group has been interested in tackling the challenge of sterically hindered cross-coupling reactions by modifying the structure of phosphorus donor ligands.[3] In 2011 we designed a phosphine ligand bearing a carbazolyl unit that can be applied in various cross-coupling reactions.[4,5] The flattened carbazolyl bottom ring takes advantage of the extended flat-wall-like rigidity to facilitate the reductive elimination process, while the sp^3-hybridized N offers weak coordination to the palladium center whenever needed during the catalytic cycle to potentially increase the catalyst longevity. Although these carbazolyl phosphines are useful ligands for promoting sterically hindered arylation processes, the difficult to scale-up synthetic pathway limits the attractiveness of these ligands for potential industrial applications. Thus, it is highly desirable to develop a simple yet scalable and low-cost protocol for the efficient synthesis of these ligands.

RESULTS AND DISCUSSION

The preparation of carbazolyl-derived ligands was accomplished in a two-step procedure: (i) formation of the key aromatic C−N bond to assemble the ligand skeleton and (ii) introduction of the phosphino moiety by electrophilic phosphination using $ClPR_2$. There have been a number of literature procedures, for instance, Pd-catalyzed Buchwald−Hartwig amination and Cu-catalyzed C−N bond formation reactions, that we can follow for arylation of the NH carbazole. Because of the economic aspect, we chose a Cu−diamine-complex-catalyzed protocol (instead of Pd-catalyzed methods[6]).[4,7] Substoichiometric amounts of CuI and *N*,*N*′-dimethylethylenediamine (DMEDA) were initially employed to facilitate the reaction between 1,2-dibromobenzene (**1**) and carbazole (**2**) to generate *N*-(2-bromophenyl)carbazole (**3a**). However, a significant amount of reduction side product **3b** was observed (essentially a **3a**:**3b** ratio of 1:1) when this catalyst system was used. We thus investigated other Cu salts for catalyzing this C−N bond-forming reaction. After probing of commonly available Cu precursors, Cu_2O was found to be better in obtaining compound **3a** selectively (Scheme 1, method A). Although it was found that this Cu_2O/DMEDA catalyst system could be used to produce several grams of ligand skeleton, it would be problematic for scaling up to more than 50 g scale because of the inefficient separation of the unwanted side product using column chromatography. Moreover, the cost of DMEDA (US$667/mol) would be too high in large-scale synthesis,[8] thus adding to the drawbacks of this procedure.

In order to avoid the use of the expensive diamine ligand, we attempted a ligand-free Cu-assisted amination method to afford the ligand skeleton (Scheme 1, method B). Here we successfully scaled up this procedure to a 30 g scale. The

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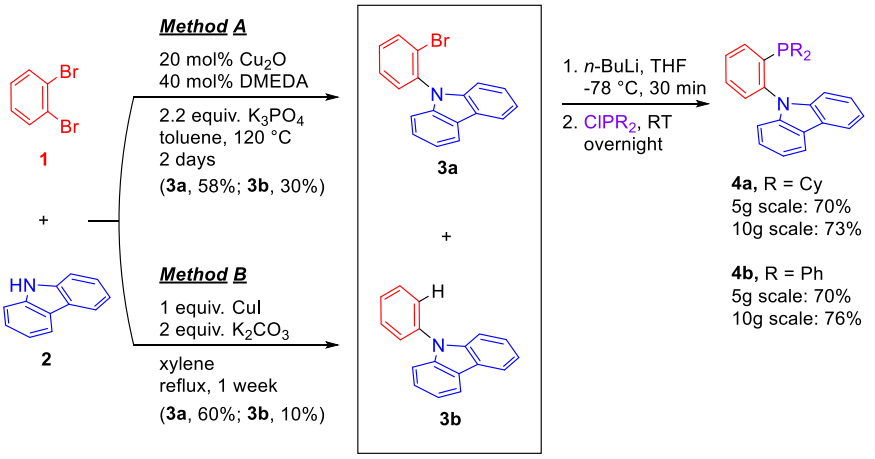
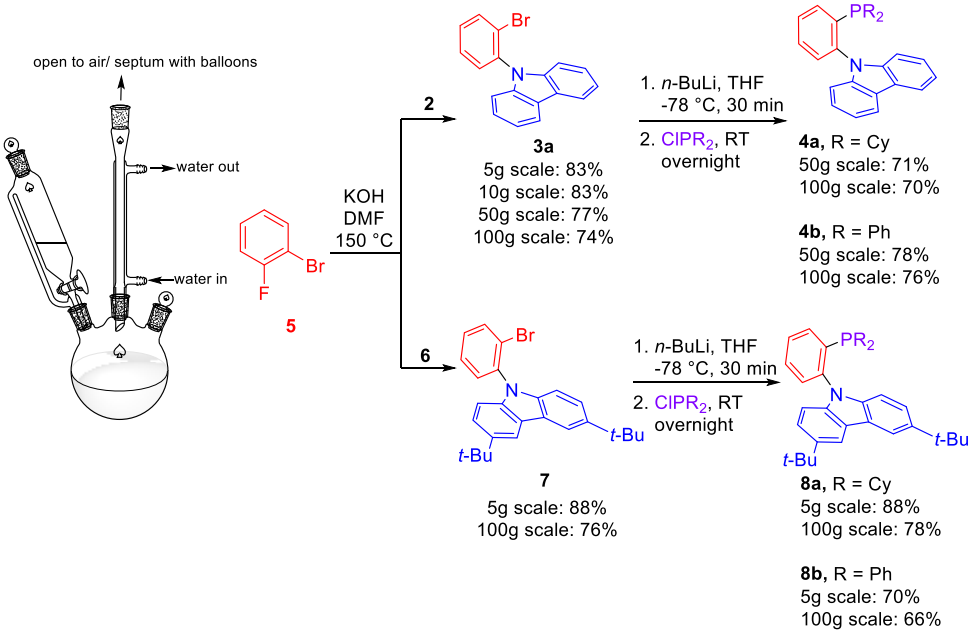
Scheme 1. Cu-Catalyzed/Assisted Synthesis of PhenCarPhos (Previous Small-Scale Synthesis and Present Large-Scale Preparation)



Scheme 2. Scaled-Up Synthesis of Ligand Precursors



desired product **3a** was shown to have a 60% GC yield. To our delight, the unwanted debrominated product **3b** seemed to be minimized in this method (~10% vs 30% in method A). Nevertheless, a notable amount of *N*-(2-iodophenyl)carbazole side product (~15% GC yield) was always found along with the desired product **3a**. This difficult-to-separate side product likely arose from halogen exchange between the aryl bromide and the CuI salt. A further drawback of this procedure is the prolonged reaction time (7 days) (Scheme 1, method B).

To simplify the purification procedure, the tedious column chromatography step was replaced by a simple gel filtration over a pad of Celite/silica gel mixture to remove a large amount of Cu residues. A further product recrystallization step to afford **3a** was thus required. However, a drop in the product yield resulted (an isolated yield of ~50% was obtained) when a larger-scale synthesis (90 mmol) was carried out. In fact, the separation of the resulting mixtures by gel filtration followed by recrystallization was problematic because of the solubility problem of the sticky gel-form crude mixtures. In order to realize a scalable synthesis of the phosphine ligands, investigation of an alternative synthetic pathway was thus demanded, as the small-scale synthetic routes shown above are not entirely feasible for bulk synthesis.

Improved Synthesis of the Ligand Precursor. There were three primary goals for our initial investigation: (i) to avoid or minimize the formation of the undesired side product **3b**; (ii) to take advantage of a metal-free and ligand-free reaction pathway under simple reaction conditions; and (iii) to simplify the purification step and thus circumvent column chromatography. Since the previously successful Cu-assisted aromatic C−N bond coupling may not be the best fit for large-scale synthesis because of the aforementioned challenges, an alternative synthetic route was investigated. A nucleophilic aromatic substitution approach was attempted to fulfill our proposed objectives. This synthetic route has the features of a simple metal-free reaction procedure and does not require inert atmosphere protection. Conventional methods for accessing aromatic amines from fluorobenzene derivatives

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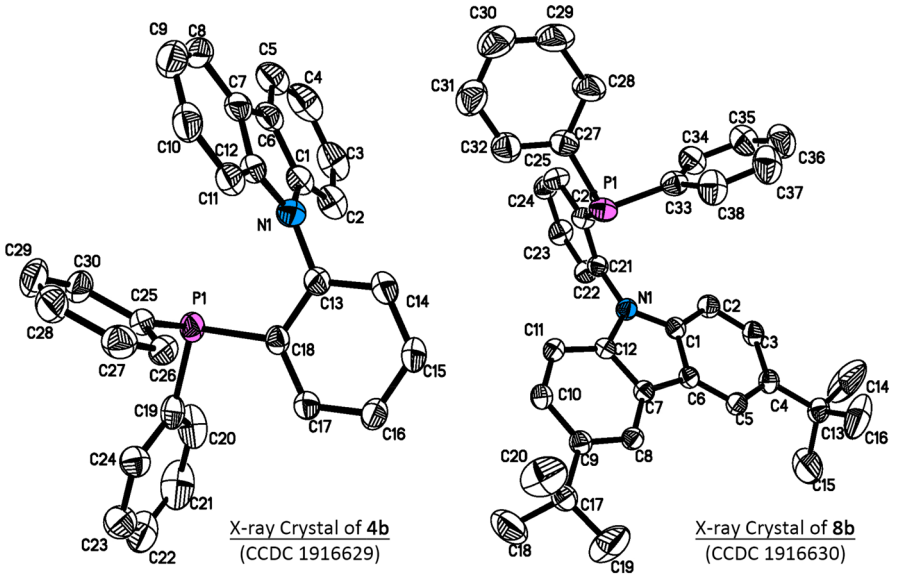
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 3. OPTEP Diagrams of 4b and 8b (All H Atoms Have Been Omitted for Clarity)



often require a strong or expensive base (e.g., LiHMDS, NaO*t*-Bu, or Cs_2CO_3) or special apparatus for harsh conditions (e.g., 190 °C, under microwave conditions) or are only favorable to highly electron-deficient fluorobenzene derivatives (e.g., hexafluorobenzene).[9] Liu and Dai recently found KOH to be an applicable base for this reaction.[9e] In our study, we attempted to use 1-bromo-2-fluorobenzene (**5**) as the starting material for the target aromatic C−N bond formation process (Scheme 2). Initial trials to probe the feasibility of this nucleophilic aromatic substitution protocol were done by varying the combination of base and solvent. Cesium carbonate, potassium carbonate, and potassium hydroxide were found to be applicable bases. Considering the chemical cost attractiveness (Cs_2CO_3, US$274/mol; K_2CO_3, US$28/mol; KOH, US$3/mol), KOH was finally chosen for readily scalable synthesis. Notably, KOH was preferably added in a portionwise manner, as the reaction becomes vigorous once the base is added. In order to minimize the loss of reactants during the base addition process, a water cooling condenser was connected to the reaction flask. An evaluation of common organic solvents revealed that *N*,*N*-dimethylformamide (DMF) was the best solvent of choice. Particularly noteworthy is that DMF solvent could be used directly as purchased without any further purification. The reaction progress was monitored by gas chromatography−mass spectrometry (GC−MS) and thin-layer chromatography (TLC). Workup procedures had to be further developed. A simple extraction was used to remove the base and DMF. Excess 1-bromo-2-fluorobenzene was recovered from the mother liquor by distillation. Crystallization of the desired products from the reaction mixtures was done using dichloromethane (DCM)/methanol with a particular ratio of 1:4. The desired product **3a** was obtained as a pale-brown solid in 83% yield with >98% purity (10 g scale) (Scheme 2). This product was directly introduced to the next step (i.e., phosphination) to afford the final ligand in >70% yield. By means of this improved synthetic route, the ligand precursor was produced on a 100 g scale in 74% yield with >98% purity. It is noteworthy that this synthetic approach was able to be extended effectively to other carbazole derivatives. For instance, 3,6-di-*tert*-butyl-9*H*-carbazole (**6**) was used in this established scale-up synthetic route to afford the corresponding ligand precursor **7** in 76% yield with >98% purity (100 g scale). The ligand structures **4b** and **8b** were unambiguously confirmed by single-crystal X-ray crystallographic analysis (Scheme 3).

Applications to Cross-Coupling Reactions. Using PhenCarPhos ligand **4a**, we investigated the sterically hindered amination of aryl chlorides. On the basis of the results of the focused reaction data set, the optimal reaction conditions for the coupling of highly sterically congested 2,6-diisopropylaniline and hindered 2-chloro-1,3-dimethylbenzene were determined to be $Pd(OAc)_2$(down to 0.05 mol %), **4a**, NaO*t*-Bu, and toluene/hexane (Scheme 4A). Further investigation showed that the reaction proceeded well on a 10 g scale using 0.1 mol % Pd catalyst to give 98% product yield. We next put our efforts into refining the workup procedure to make it more cost-effective and require fewer unit operations. The initial workup step focused on extraction of the desired product from the reaction mixture by the addition of water and 10 M hydrochloric acid. The acid neutralized the unreacted 2,6-diisopropylaniline, and the products were essentially in the organic phase. By simple filtration and concentration, sterically hindered *N*-(2,6-diisopropylphenyl)-2,6-dimethylaniline (**9**) was obtained in 98% yield with ∼95% purity on a 10 g scale (Scheme 4A). In order to further show the versatility of this ligand series, the carbazolylphosphines were examined in scaled-up Suzuki−Miyaura coupling reaction. Griseofulvin, an antifungal agent that is commonly used to treat dermatophytes, coupled smoothly with *o*-tolylboronic acid under the Pd-**8a** catalyst system to give product **10** in 93% yield (Scheme 4B, top). It should be noted that in a 10 g scale experiment, the coupling product could even be obtained by a simple extraction (∼95% purity as judged by GC). As another example, 2,3,4,5,6-pentafluoro-2′,6′-dimethyl-1,1′-biphenyl (**11**) was synthesized in 78% yield (Scheme 4B, bottom). On a 10 g scale, a product purity of ∼96% was achieved via simple extraction with 6 M HCl and 1 M NaOH followed by recrystallization.

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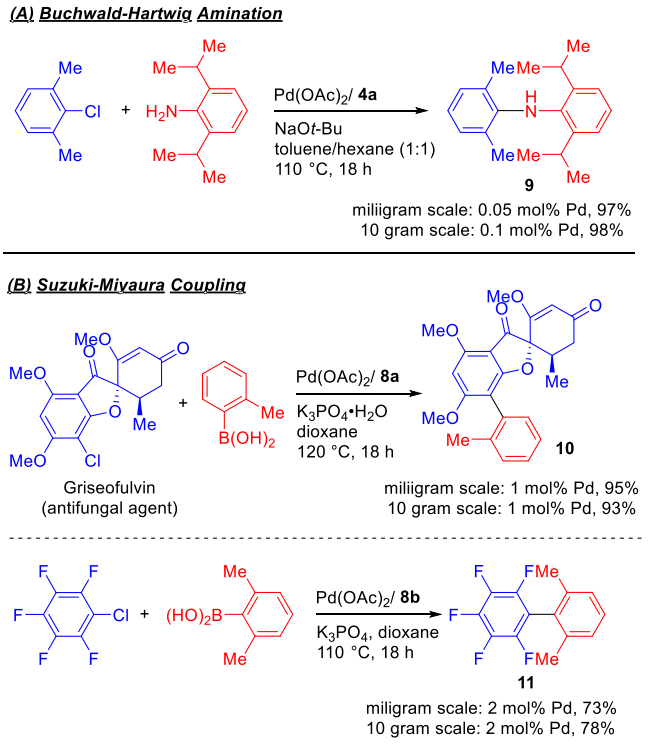
Scheme 4. Applications of the Carbazolyl-Derived Phosphine Ligands



CONCLUSION

We have attempted to optimize the reaction conditions for Cu-catalyzed and -assisted C(sp^2)−N bond construction processes for scaled-up synthesis. Unfortunately, the aforementioned protocols remained unfavorable, as the necessity of using the DMEDA ligand or a stoichiometric amount of Cu salt, leading to purification problem. An additional drawback of these routes included the difficult to separate debrominated side product that often exists. To our delight, we established a complementary protocol for carbazole arylation using a nucleophilic aromatic substitution pathway. The synthetic route has the features of being metal-free, requiring only an inexpensive base (e.g., KOH), and avoiding the use of chromatographic purification. This simple protocol was found to be scalable up to 100 g without difficulties, which enhances the attractiveness of this tunable ligand family. Finally, the carbazolyl-derived phosphines were found to be able to efficiently promote arylation processes (10 g scale) using sterically hindered 2,6-disubstituted aryl chlorides as the representative electrophilic partners. Further explorations of this carbazolyl ligand series are underway.

EXPERIMENTAL SECTION

General Considerations. Unless otherwise noted, all of the reagents were purchased from commercial suppliers and used without further purification. Toluene, xylene, 1,4-dioxane, and tetrahydrofuran (THF) were freshly distilled from sodium and sodium benzophenone ketyl under nitrogen.[10] DMF was used as received without any further purification. Hexane was freshly distilled from calcium hydride under nitrogen before use. All of the bases were used as received without grinding. A new bottle of *n*-butyllithium was used (note: since the concentration of *n*-BuLi from old bottles may vary, titration is highly recommended prior to use). All of the Pd-catalyzed cross-coupling/arylation reactions were performed in a resealable screw-capped Schlenk flask (approximate volume 250 mL) in the presence of a Teflon-coated magnetic stir bar. TLC was performed on precoated silica gel 60 F_{254} plates. Silica gel (70−230 and 230−400 mesh) was used for column chromatography. Melting points were recorded on an uncorrected instrument. ^{1}H NMR spectra were recorded on a 400 or 500 MHz spectrometer. Spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ 7.26) or to tetramethylsilane (TMS) (δ 0.00) as an internal standard. Chemical shifts (δ) are reported in parts per million downfield from TMS. ^{13}C NMR spectra were recorded on a 100 or 125 MHz spectrometer, and the spectra were referenced to $CDCl_3$ (δ 77.0, the middle peak). ^{31}P NMR spectra were referenced to external 85% H_3PO_4. Coupling constants (J) are reported in hertz. Mass spectrometry (EI-MS and ESI-MS) was performed on a mass spectrometer. High-resolution mass spectrometry (HRMS) was performed on a Q Exactive Focus Orbitrap mass spectrometer with an atmospheric-pressure chemical ionization (APCI) source. GC−MS analysis was conducted on a GCD system using a 30 m × 0.25 mm column. GC yields of products were obtained on the basis of authentic sample/dodecane calibration standards from the GC-FID system. Compounds described in the literature were characterized by comparison of their ^{1}H and/or ^{13}C NMR spectra to the previously reported data. The procedures in this section are representative, and thus, the yields may differ from those reported above.

9-(2-Bromophenyl)-9*H*-carbazole (3a).[4a] *Method A: Cu/DMEDA-Catalyzed C−N Bond Formation.* Carbazole (50 mmol, 8.35 g), Cu_2O (10 mmol, 1.43 g), K_3PO_4 (110 mmol, 23.4 g), and a Teflon-coated magnetic stir bar were charged to a two-neck round-bottom flask equipped with a condenser and fitted with a septum. The system was carefully evacuated and backfilled with nitrogen (three cycles). 1,2-Dibromobenzene (100 mmol, 12 mL, 2.0 equiv), DMEDA (20 mmol, 2.15 mL), and distilled dry toluene were added. The reaction mixture was allowed to heat in a preheated oil bath (120 °C) for 2 days. After the completion of the reaction, the crude mixture was poured into 1.0 M aqueous ammonium hydroxide and extracted with DCM. The organic phase was separated, and the aqueous layer was further extracted with DCM. The combined organic phases were concentrated under reduced pressure. The crude product was purified by flash column chromatography (9:1 hexane/EtOAc, R_f = 0.8) to afford 9-(2-bromophenyl)-9*H*-carbazole (**3a**) as white solid (9.3 g, 58% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, J = 7.5 Hz, 2H), 7.89 (d, J = 8.0 Hz, 1H), 7.57−7.50 (m, 2H), 7.44 (t, J = 7.5 Hz, 3H), 7.33 (t, J = 7.3 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 136.7, 134.2, 131.1, 130.1, 128.8, 125.9, 123.8, 123.2, 120.3, 120.0, 109.9.

Method B: Ligand-Free Cu-Catalyzed C−N Bond Formation (Traditional Purification Method). Carbazole (200 mmol, 33.4 g), CuI (200 mmol, 38.1 g), K_2CO_3 (400 mmol, 55.2 g), and a Teflon-coated magnetic stir bar were charged to a two-neck round-bottom flask (2 L) equipped with a condenser and fitted with a septum. The system was carefully evacuated and backfilled with nitrogen (three cycles). 1,2-Dibromobenzene (400 mmol, 48.2 mL) and dry xylene (1.5 L) were added by syringe via the septum. The septum was switched with a stopper, and the reaction mixture was allowed to reflux in a preheated oil bath (185 °C) for 1 week. After completion of the reaction, the copper powder was filtered off

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

by Celite, and the xylene was removed by distillation under high vacuum. The crude product was purified by flash column chromatography on silica gel (230−400 mesh) to afford the product as a white solid (38.5 g, 60% yield).

Method B: Ligand-Free Cu-Catalyzed C−N Bond Formation (Simplified Purification Method). Carbazole (100 mmol, 16.7 g), CuI (100 mmol, 19.1 g), K_2CO_3 (200 mmol, 27.6 g), and a Teflon-coated magnetic stir bar were charged to a two-neck round-bottom flask (1 L) equipped with a condenser and fitted with a septum. The system was carefully evacuated and backfilled with nitrogen (three cycles). 1,2-Dibromobenzene (200 mmol, 24.1 mL) and nondistilled xylene (750 mL) were added by syringe via the septum. The septum was switched with a stopper, and the reaction mixture was allowed to reflux in a preheated oil bath (185 °C) for 1 week. After completion of the reaction, the copper powder was filtered off by Celite, and the xylene was removed by distillation under high vacuum. The crude product was then filtered by a short silica pad with hexane to remove unreacted 1,2-dibromobenzene. The silica gel was then washed with 10:1 hexane/EtOAc. The filtrate was concentrated under rotary evaporation, and recrystallization was carried out with hexane/DCM to afford the desired product as a white solid (16.0 g, 50% yield).

Improved Synthesis and Purification Method. Carbazole (1 equiv), KOH (3 equiv), and a Teflon-coated magnetic stir bar were charged to a three-neck round-bottom flask equipped with a condenser and dropping funnel under an atmosphere of air. DMF was added, and the reaction mixture was kept stirring at room temperature until all of the KOH and carbazole were dissolved. The reaction mixture was allowed to heat in a heating mantle/preheated oil bath (150−155 °C), and 1-bromo-2-fluorobenzene (4 equiv) was added slowly through the dropping funnel. After additional KOH (2 equiv) was added to the reaction every 1 h (the total reaction time was 5−12 h depending on the synthetic scale). The reaction was monitored by GC−MS and TLC. The crude mixture was poured into water and extracted with DCM to remove KOH and DMF. The organic phase was separated, and the aqueous layer was further extracted with DCM. The combined organic phases were concentrated under rotary evaporation. The unreacted 1-bromo-2-fluorobenzene was then removed from the residue by distillation or heating under vacuum. Crystallization was carried out by adding 1:4 DCM/methanol to afford pale brown solid as desired product (74−83%).

5 g scale: Carbazole (20 mmol, 3.3 g), KOH (60 mmol, 3.4 g, start of reaction; 40 mmol, 2.2 g, first hour; 40 mmol, 2.2 g, second hour; 40 mmol, 2.2 g, third hour; 40 mmol, 2.2 g, fourth hour; total 220 mmol, 12.0 g), DMF (50 mL), 1-bromo-2-fluorobenzene (80 mmol, 8.7 mL), total reaction time of 5 h, reaction temperature of 150 °C, 83% yield (5.3 g).

10 g scale: Carbazole (50 mmol, 8.4 g), KOH (150 mmol, 8.4 g, start of reaction; 100 mmol, 5.6 g, first hour; 100 mmol, 5.6 g, second hour; 100 mmol, 5.6 g, third hour; 100 mmol, 5.6 g, fourth hour; total 550 mmol, 31.0 g), DMF (200 mL), 1-bromo-2-fluorobenzene (200 mmol, 21.9 mL), total reaction time of 6 h, reaction temperature of 155 °C, 83% yield (13.3 g).

50 g scale: Carbazole (220 mmol, 36.8 g), KOH (660 mmol, 37.0 g, start of reaction; 440 mmol, 24.7 g, first hour; 440 mmol, 24.7 g, second hour; 440 mmol, 24.7 g, third hour; 440 mmol, 24.7 g, fourth hour; 440 mmol, 24.7 g, fifth hour; 440 mmol, 24.7 g, sixth hour; total 3.3 mol, 185.0 g), DMF (1.5 L), 1-bromo-2-fluorobenzene (880 mmol, 96.2 mL), total reaction time of 12 h, reaction temperature of 155 °C, 77% yield (54.4 g).

100 g scale: Carbazole (0.52 mol, 86.9 g), KOH (1.56 mol, 87.5 g, start of reaction; 1.04 mol, 58.3 g, first hour; 1.04 mol, 58.3 g, second hour; 1.04 mol, 58.3 g, third hour; 1.04 mol, 58.3 g, fourth hour; 1.04 mol, 58.3 g, fifth hour; 1.04 mol, 58.3 g, sixth hour; total 7.8 mol, 437.0 g), DMF (2.5 L), 1-bromo-2-fluorobenzene (1.56 mol, 170 mL), total reaction time of 12 h, reaction temperature of 155 °C, 74% yield (123.0 g).

General Procedure for the Synthesis of Phosphine Ligands. The ligand precursor (1 equiv) was dissolved in freshly distilled THF at room temperature under a nitrogen atmosphere. The solution was cooled to −78 °C in a dry ice/acetone bath. Titrated *n*-BuLi (1.1 equiv) was added dropwise through a dropping funnel, and the reaction mixture was stirred for 30 min at −78 °C. Chlorodicyclohexylphosphine ($ClPCy_2$) or chlorodiphenylphosphine ($ClPPh_2$) (1.1 equiv) in THF was added. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The solvent was removed under reduced pressure, and the mixture was crystallized by addition of DCM/methanol (with a ratio of 1:6, depending on the scale). The solid products were filtered and successively washed with cold MeOH. The product was dried under vacuum.

9-(2-(Dicyclohexylphosphino)phenyl)-9*H*-carbazole (4a).[4a] The general procedure for the synthesis of phosphine ligands was followed. Precursor **3a** and $ClPCy_2$ were used to afford 9-(2-(dicyclohexylphosphino)phenyl)-9*H*-carbazole (**4a**) as a white solid. ^{1}H NMR (500 MHz, C_6D_6) δ 8.08 (d, J = 7.5 Hz, 2H), 7.56 (d, J = 7.5 Hz, 1H), 7.36 (t, J = 8.2 Hz, 2H), 7.24 (t, J = 7.7 Hz, 2H), 7.19 (t, J = 8.0 Hz, 1H), 7.16−7.08 (m, 3H), 1.69−1.51 (m, 10H), 1.11−0.92 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 144.2, 142.92, 138.42, 138.2, 134.2, 134.2, 130.4, 130.4, 130.3, 125.6, 123.7, 120.6, 119.9, 111.1, 111.1, 34.4, 34.2, 30.6, 30.4, 30.0, 29.9, 27.5, 27.4, 27.4, 27.3, 26.6; ^{31}P NMR (162 MHz, C_6D_6) δ −14.682.

5 g scale: **3a** (20 mmol, 6.4 g), $ClPCy_2$ (22 mmol, 4.86 mL), THF (50 mL), 70% yield (6.14 g).

10 g scale: **3a** (35 mmol, 11.2 g), $ClPCy_2$ (38.5 mmol, 8.50 mL), THF (100 mL), 73% yield (11.2 g).

50 g scale: **3a** (165 mmol, 53.0 g), $ClPCy_2$ (181.5 mmol, 40 mL), THF (600 mL), 71% yield (51.4 g).

100 g scale: **3a** (350 mmol, 112.4 g), $ClPCy_2$ (385 mmol, 85 mL), THF (1 L), 70% yield (107.6 g).

9-(2-(Diphenylphosphino)phenyl)-9*H*-carbazole (4b).[4a] The general procedure for the synthesis of phosphine ligands was followed. Precursor **3a** and $ClPPh_2$ were used to afford 9-(2-(diphenylphosphino)phenyl)-9*H*-carbazole (**4b**) as a white solid. ^{1}H NMR (500 MHz, C_6D_6) δ 8.03−8.01 (m, 2H), 7.40−7.38 (m, 1H), 7.22−7.17 (m, 4H), 7.15−7.12 (m, 4H), 7.04−7.02 (m, 2H), 6.96−6.88 (m, 8H); ^{13}C NMR (125 MHz, C_6D_6) δ 142.3, 142.2, 142.0, 140.9, 140.7, 136.9, 136.7, 135.1, 134.2, 134.1, 130.6, 130.4, 130.4, 129.0, 128.8, 128.6, 128.5, 125.8, 123.7, 120.4, 119.9, 110.7, 110.7; ^{31}P NMR (162 MHz, C_6D_6) δ −16.263.

5 g scale: **3a** (20 mmol, 6.4 g), $ClPPh_2$ (22 mmol, 4.06 mL), THF (50 mL), 70% yield (6.0 g).

10 g scale: **3a** (35 mmol, 11.2 g), $ClPPh_2$ (38.5 mmol, 7.11 mL), THF (100 mL), 76% yield (11.4 g).

50 g scale: **3a** (165 mmol, 53.0 g), $ClPPh_2$ (181.5 mmol, 33.5 mL), THF (600 mL), 78% yield (55.0 g).

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

100 g scale: **3a** (320 mmol, 102.7 g), $ClPPh_2$ (352 mmol, 65 mL), THF (1 L), 76% yield (103.8 g).

9-(2-Bromophenyl)-3,6-di-*tert*-butyl-9*H*-carbazole (7).[4b] The general procedure of the improved synthetic method was followed. 3,6-Di-*tert*-butyl-9*H*-carbazole (**6**) (1 equiv), KOH (total of 10 equiv), and 1-bromo-2-fluorobenzene (4 equiv) were mixed in DMF and heated at 155 °C for a total of 12 h. After extraction and recrystallization, 9-(2-bromophenyl)-3,6-di-*tert*-butyl-9*H*-carbazole (**7**) was obtained in 76−88% yield as a pale-yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 2H), 7.87 (d, J = 8.0 Hz, 1H), 7.52−7.45 (m, 4H), 7.39 (t, J = 7.8 Hz, 1H), 7.01 (d, J = 8.5 Hz, 2H), 1.48 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.7, 139.3, 137.3, 134.1, 131.0, 129.8, 128.7, 123.7, 123.5, 123.2, 116.3, 109.4, 34.7, 32.0.

5 g scale: **6** (15 mmol, 4.2 g), KOH (45 mmol, 2.52 g, start of reaction; 30 mmol, 1.68 g, first hour; 30 mmol, 1.68 g, second hour; 30 mmol, 1.68 g, third hour; 30 mmol, 1.68 g, fourth hour; total 165 mmol, 9.3 g), DMF (50 mL), 1-bromo-2-fluorobenzene (60 mmol, 6.6 mL), total reaction time of 8 h, reaction temperature of 155 °C, 88% yield (5.7 g).

100 g scale: **6** (0.35 mol, 97.7 g), KOH (1.05 mol, 58.9 g, start of reaction; 0.7 mol, 39.3 g, first hour; 0.7 mol, 39.3 g, second hour; 0.7 mol, 39.3 g, third hour; 0.7 mol, 39.3 g, fourth hour; 0.7 mol, 39.3 g, fifth hour; 0.7 mol, 39.3 g, sixth hour; total 5.25 mol, 295.0 g), DMF (2.5 L), 1-bromo-2-fluorobenzene (1.4 mol, 153 mL), total reaction time of 12 h, reaction temperature of 155 °C, 76% yield (115 g).

3,6-Di-*tert*-butyl-9-(2-(dicyclohexylphosphino)-phenyl)-9*H*-carbazole (8a).[4b] The general procedure for the synthesis of phosphine ligands was followed. Precursor **7** and $ClPCy_2$ were used to afford 3,6-di-*tert*-butyl-9-(2-(dicyclohexylphosphino)phenyl)-9*H*-carbazole (**8a**) as a white solid. ^{1}H NMR (500 MHz, C_6D_6) δ 8.38 (s, 2H), 7.58 (d, J = 7.5 Hz, 2H), 7.52 (d, J = 9.0 Hz, 1H), 7.20 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 7.0 Hz, 2H), 1.73−1.53 (m, 12H), 1.42 (s, 18H), 1.18−0.96 (m, 10H); ^{13}C NMR (125 MHz, C_6D_6) δ 145.0, 144.8, 142.4, 138.4, 138.2, 134.0, 134.0, 130.3, 130.3, 128.3, 128.1, 127.9, 124.0, 123.5, 116.6, 110.8, 110.8, 34.8, 34.4, 34.2, 32.2, 30.4, 30.3, 30.0, 30.0, 27.6, 27.5, 27.4, 27.4, 27.4, 26.6; ^{31}P NMR (162 MHz, C_6D_6) δ −14.598.

5 g scale: **7** (12 mmol, 5.2 g), $ClPCy_2$ (13.2 mmol, 2.91 mL), THF (20 mL), 88% yield (5.83 g).

100 g scale: **7** (250 mmol, 108.4 g), $ClPCy_2$ (275 mmol, 60.7 mL), THF (800 mL), 78% yield (107.6 g).

3,6-Di-*tert*-butyl-9-(2-(diphenylphosphino)phenyl)-9*H*-carbazole (8b).[11] The general procedure for the synthesis of phosphine ligands was followed. Precursor **7** and $ClPPh_2$ were used to afford 3,6-di-*tert*-butyl-9-(2-(diphenylphosphino)phenyl)-9*H*-carbazole (**8b**) as a white solid. ^{1}H NMR (500 MHz, C_6D_6) δ 8.31 (d, J = 2.0 Hz, 2H), 7.44−7.41 (m, 1H), 7.34 (dd, J = 8.5, 2 Hz, 2H), 7.19−7.17 (m, 4H); 7.10−7.03 (m, 3H), 6.98−6.92 (m, 8H), 1.41 (s, 18H); ^{13}C NMR (125 MHz, C_6D_6) δ 142.3, 141.1, 137.1, 137.0, 135.0, 134.3, 134.2, 130.6, 130.4, 130.4, 128.9, 128.7, 128.5, 128.5, 128.3, 123.9, 123.6, 116.3, 110.4, 110.4, 34.7, 32.2; ^{31}P NMR (162 MHz, C_6D_6) δ −16.202.

5 g scale: **7** (15 mmol, 6.5 g), $ClPPh_2$ (16.5 mmol, 3.05 mL), THF (30 mL), 70% yield (5.67 g).

100 g scale: **7** (300 mmol, 130.0 g), $ClPPh_2$ (330 mmol, 61 mL), THF (1 L), 66% yield (106.7 g).

***N*-(2,6-Diisopropylphenyl)-2,6-dimethylaniline (9).**[12] $Pd(OAc)_2$ (0.1 mol %, 0.025 mmol, 0.0056 g), **4a** (0.4 mol %, 0.1 mmol, 0.0439 g), and NaO*t*-Bu (150 mmol, 14.4 g) were loaded into a Schlenk flask equipped with a Teflon-coated magnetic stir bar. The flask was evacuated and flushed with nitrogen for three cycles. 2-Chloro-1,3-dimethylbenzene (50 mmol, 6.63 mL), 2,6-diisopropylaniline (100 mmol, 18.9 mL), toluene (25 mL), and hexane (25 mL) were added with stirring at room temperature, and stirring was continued for several minutes. The flask was then placed into a preheated oil bath (110 °C) and stirred for 18 h. After completion of the reaction as judged by GC−MS and TLC, the reaction flask was allowed to cool to room temperature, and 50 mL of water was added to the mixture. The resulting mixture was extracted with EtOAc, and the organic layer was collected and extracted with 20 mL of aqueous 10 M hydrochloric acid at least 4 times to remove the unreacted 2,6-diisopropylaniline (as monitored by TLC). The solvent was then removed by rotary evaporation to afford the desired product (98% yield, 15.7 g, 16.1 mL) as a dark-brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16−7.10 (m, 3H), 6.94 (d, J = 7.5 Hz, 2H), 6.72 (t, J = 7.5 Hz, 1H), 3.17−3.12 (m, 2H), 1.98 (s, 6H), 1.11 (d, J = 7.0 Hz, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 143.1, 138.8, 129.5, 125.6, 124.8, 123.2, 119.6, 28.0, 23.4, 19.3.

(2*S*,6′*R*)-2′,4,6-Trimethoxy-6′-methyl-7-(*o*-tolyl)-3*H*-spiro[benzofuran-2,1′-cyclohexan]-2′-ene-3,4′-dione (10). $Pd(OAc)_2$ (1 mol %, 0.3 mmol, 0.067 g), **8a** (4 mol %, 1.2 mmol, 0.66 g), griseofulvin (30 mmol, 10.58 g), *o*-tolylboronic acid (60 mmol, 8.16 g), and $K_3PO_4{\cdot}H_2O$ (90 mmol, 20.7 g) were loaded into a Schlenk flask equipped with a Teflon-coated magnetic stir bar. The flask was evacuated and flushed with nitrogen for three cycles. Dioxane (50 mL) was added with stirring at room temperature, and stirring was continued for several minutes. The flask was then placed into a preheated oil bath (120 °C) and stirred for 24 h. After completion of the reaction as judged by GC-MS and TLC, the reaction flask was allowed to cool to room temperature, and 50 mL of water was added to the mixture. The resulting mixture was extracted with EtOAc, and the organic layer was collected and extracted with 1 M NaOH solution at least three times. Water and brine were further used for extraction. The organic layer was concentrated by rotary evaporation to afford the desired product (93% yield, 11.4 g) as a pale-yellow solid (mp 120.0−122.2 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 4.0 Hz, 2H), 7.22−7.15 (m, 1H), 6.17 (s, 1H), 5.45 (s, 1H), 4.01 (s, 3H), 3.86 (s, 3H), 3.57 (d, J = 15.5 Hz, 3H), 3.04 (dd, J = 13.5, 16.5 Hz, 1H), 2.68−2.63 (m, 1H), 2.36−2.31 (m, 1H), 2.18 (d, J = 2 Hz, 3H), 0.94−0.93 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.2, 197.2, 193.0, 171.6, 171.6, 171.5, 166.5, 166.5, 158.7, 158.6, 137.9, 137.6, 131.0, 130.9, 130.6, 130.6, 129.8, 129.7, 128.0, 128.0, 125.4, 125.4, 106.8, 104.3, 104.2, 103.8, 89.6, 88.6, 88.5, 77.3, 77.0, 76.7, 56.4, 56.4, 56.1, 56.1, 39.9, 39.8, 36.2, 36.0, 19.8, 19.5, 14.1, 14.1; HRMS (ESI$^+$) m/z [M + Na]$^+$ calcd for $C_{24}H_{25}O_6$ 431.14651, found 431.14631.

2,3,4,5,6-Pentafluoro-2′,6′-dimethyl-1,1′-biphenyl (11).[13] $Pd(OAc)_2$ (2 mol %, 1.2 mmol, 0.27 g), **8b** (8 mol %, 4.8 mmol, 2.59 g), 2,6-dimethylphenylboronic acid (120 mmol, 18.0 g), and K_3PO_4 (180 mmol, 38.2 g) were loaded into a Schlenk flask equipped with a Teflon-coated magnetic stir bar. The flask was evacuated and flushed with nitrogen for three cycles. Chloropentafluorobenzene (60 mmol, 7.75 mL) and dioxane (60 mL) were added with stirring at room temperature, and stirring was continued for several minutes. The flask was then placed into a preheated oil bath (110 °C)

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

and stirred for 18 h. After completion of the reaction as judged by GC-MS and TLC, the reaction flask was allowed to cool to room temperature, and 50 mL of water was added to the mixture. The resulting mixture was extracted with diethyl ether, and the organic layer was collected and extracted with 200 mL of aqueous 6 M hydrochloric acid at least three times followed by 200 mL of 1 M sodium hydroxide solution at least three times. The organic layer was further washed with water and brine. The solvent was then removed by rotary evaporation to afford a yellow oil. After cooling with an ice−water bath, the desired product (78% yield, 12.7 g) was obtained by recrystallization as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 2H), 2.10 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8−144.6 (m), 142.8−142.7 (m), 141.8−141.5 (m), 139.7−139.5 (m), 138.9−138.6 (m), 137.4, 136.9−136.6 (m), 129.4, 127.7, 125.6, 20.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ −140.1 to −140.2 (dd, J = 23.5, 9.4 Hz, 2F), −155.2 (t, J = 18.8 Hz, 1F), −161.9 to −162.0 (m, 2F).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00246.

Copies of ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra and crystallographic data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: fykwong@cuhk.edu.hk.

ORCID

Fuk Yee Kwong: 0000-0001-9105-1740

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Notes

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■ REFERENCES

(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vols. *1* and *2*. (b) Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (c) *Metal-Catalyzed Cross-Coupling Reactions and More*; de Meijere, A., Bräse, S., Oestreich, M., Eds.; Wiley-VCH: Weinheim, Germany, 2014; Vols. *1*−*3*. (d) *New Trends in Cross-Coupling: Theory and Applications*; Colacot, T. J., Ed.; RSC Publishing: Cambridge, U.K., 2015. (e) Xu, G.; Senanayake, C. H.; Tang, W. P-Chiral Phosphorus Ligands Based on a 2,3-Dihydrobenzo[*d*][1,3]-oxaphosphole Motif for Asymmetric Catalysis. *Acc. Chem. Res.* **2019**, *52*, 1101.

(2) (a) Martin, R.; Buchwald, S. L. Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling Reactions Employing Dialkylbiaryl Phosphine Ligands. *Acc. Chem. Res.* **2008**, *41*, 1461. (b) Wong, S. M.; So, C. M.; Kwong, F. Y. The recent development of phosphine ligands derived from 2-phosphino-substituted heterocycles and their applications in palladium-catalyzed cross-coupling reactions. *Synlett* **2012**, *23*, 1132. (c) Wong, S. M.; Yuen, O. Y.; Choy, P. Y.; Kwong, F. Y. When Cross-Coupling Partners Meet Indolyphosphines. *Coord. Chem. Rev.* **2015**, *293*−*294*, 158. (d) Li, C.; Chen, D.; Tang, W. Addressing the Challenges in Suzuki-Miyaura Cross-Couplings by Ligand Design. *Synlett* **2016**, *27*, 2183.

(3) For selected references, see: (a) So, C. M.; Chow, W. K.; Choy, P. Y.; Lau, C. P.; Kwong, F. Y. Remarkably Effective Phosphanes Simply with a PPh_2 Moiety: Application to Pd-Catalysed Cross-Coupling Reactions for Tetra-*ortho*-substituted Biaryl Syntheses. *Chem. - Eur. J.* **2010**, *16*, 7996. (b) Yeung, P. Y.; Tsang, C. P.; Kwong, F. Y. Efficient cyanation of aryl bromides with $K_4[Fe(CN)_6]$ catalyzed by a palladium-indolylphosphine complex. *Tetrahedron Lett.* **2011**, *52*, 7038. (c) Yeung, P. Y.; Chung, K. H.; Kwong, F. Y. Palladium-Catalyzed Decarboxylative Arylation of Potassium Cyanoacetate: Synthesis of Diaryl Nitriles from Aryl Halides. *Org. Lett.* **2011**, *13*, 2912. (d) Chow, W. K.; So, C. M.; Lau, C. P.; Kwong, F. Y. Palladium-Catalyzed Borylation of Aryl Mesylates and Tosylates and Their Applications in One-Pot Sequential Suzuki-Miyaura Biaryl Synthesis. *Chem. - Eur. J.* **2011**, *17*, 6913. (e) Lee, D. S.; Choy, P. Y.; So, C. M.; Wang, J.; Lau, C. P.; Kwong, F. Y. Palladium-catalyzed direct arylation of polyfluoroarenes with aryl tosylates and mesylates. *RSC Adv.* **2012**, *2*, 9179. (f) Fu, W. C.; So, C. M.; Kwong, F. Y. Palladium-Catalyzed Phosphorylation of Aryl Mesylates and Tosylates. *Org. Lett.* **2015**, *17*, 5906. (g) Kuang, F.; Zhou, Y.; Su, Q.; Cai, P. Method for preparing high-steric hindrance arylboronic acid ester compound. CN104327106B, 2017.

(4) (a) To, S. C.; Kwong, F. Y. Highly efficient carbazolyl-derived phosphine ligands: Application to sterically hindered biaryl couplings. *Chem. Commun.* **2011**, *47*, 5079. (b) Fu, W. C.; Zhou, Z.; Kwong, F. Y. Preparation of a Highly Congested Carbazoyl-Derived P,N-Type Phosphine Ligand for Acetone Monoarylations. *Organometallics* **2016**, *35*, 1553. (c) Fu, W. C.; Zhou, Z.; Kwong, F. Y. A benzo[*c*]carbazolyl-based phosphine ligand for Pd-catalyzed tetra-*ortho*-substituted biaryl syntheses. *Org. Chem. Front.* **2016**, *3*, 273. (d) Lai, W. I.; Leung, M. P.; Choy, P. Y.; Kwong, F. Y. Sterically Hindered Amination of Aryl Chlorides Catalyzed by a New Carbazolyl-Derived P,N-Ligand-Composed Palladium Complex. *Synthesis* **2019**, *51*, 2678.

(5) Gurung, S. K.; Thapa, S.; Kafle, A.; Dickie, D. A.; Giri, R. Copper-Catalyzed Suzuki-Miyaura Coupling of Arylboronate Esters: Transmetalation with (PN)CuF and Identification of Intermediates. *Org. Lett.* **2014**, *16*, 1264.

(6) Our publications about C−N bond formation: (a) Kwong, F. Y.; Buchwald, S. L. Mild and Efficient Copper-Catalyzed Amination of Aryl Bromides with Primary Alkylamines. *Org. Lett.* **2003**, *5*, 793. (b) Chen, G.; Lam, W. H.; Fok, W. S.; Lee, H. W.; Kwong, F. Y. Easily accessible benzamide-derived P, O ligands (Bphos) for palladium-catalyzed carbon-nitrogen bond-forming reactions. *Chem. - Asian J.* **2007**, *2*, 306. (c) So, C. M.; Lau, C. P.; Zhou, Z.; Kwong, F. Y. Palladium-catalyzed amination of aryl mesylates. *Angew. Chem., Int. Ed.* **2008**, *47*, 6402. (d) Yang, Q.; Choy, P. Y.; Fu, W. C.; Fan, B.; Kwong, F. Y. Copper-Catalyzed Oxidative C-H Amination of Tetrahydrofuran with Indole/ Carbazole Derivatives. *J. Org. Chem.* **2015**, *80*, 11193. (e) Fu, W. C.; Zheng, B.; Zhao, Q.; Chan, W. T. K.; Kwong, F. Y. Cascade Amination and Acetone Monoarylation with Aryl Iodides by Palladium/ Norbornene Cooperative Catalysis. *Org. Lett.* **2017**, *19*, 4335. (f) Choy, P. Y.; Chung, K. H.; Yang, Q.; So, C. M.; Sun, R. W.-Y.; Kwong, F. Y. A General Palladium-Phosphine Complex for Exploring Aryl Tosylates in N-arylation of amines: Scope and Limitation. *Chem. - Asian J.* **2018**, *13*, 2465.

(7) Antilla, J. C.; Klapars, A.; Buchwald, S. L. The Copper-Catalyzed *N*-Arylation of Indoles. *J. Am. Chem. Soc.* **2002**, *124*, 11684.

(8) According to the 2019 Aldrich catalog, the price of DMEDA is US$188.83 for 25 g.

(9) (a) Diness, F.; Fairlie, D. P. Catalyst-Free N-Arylation Using Unactivated Fluorobenzenes. *Angew. Chem., Int. Ed.* **2012**, *51*, 8012. (b) Diness, F.; Begtrup, M. Sequential Direct S_NAr Reactions of Pentafluorobenzenes with Azole or Indole Derivatives. *Org. Lett.* **2014**, *16*, 3130. (c) Kong, X.; Zhang, H.; Xiao, Y.; Cao, C.; Shi, Y.; Pang, G. Effective, transition metal free and selective C-F activation under mild conditions. *RSC Adv.* **2015**, *5*, 7035. (d) Tao, S.; Liu, N.; Dai, B. One-pot two-step synthesis of N-arylcarbazole-based skeleton. *RSC Adv.* **2016**, *6*, 43250. (e) Wang, L.; Ji, E.; Liu, N.; Dai, B. Site-Selective N-Arylation of Carbazoles with Halogenated Fluorobenzenes. *Synthesis* **2016**, *48*, 737.

DOI: 10.1021/acs.oprd.9b00246
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

(10) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford. U.K., 1996.
(11) Li, Q.; Wei, Q.; Xie, P.; Liu, L.; Zhong, X.-X.; Li, F.-B.; Zhu, N.-Y.; Wong, W.-Y.; Chan, W. T.-K.; Qin, H.-M.; Alharbi, N. S. Synthesis, characterization, and luminescent properties of three-coordinate copper(I) halide complexes containing a carbazolyl monodentate phosphine ligand. *J. Coord. Chem.* **2018**, *71*, 4072.
(12) Lee, D.-H.; Taher, A.; Hossain, S.; Jin, M.-J. An efficient and general method for the Heck and Buchwald-Hartwig coupling reactions of aryl chlorides. *Org. Lett.* **2011**, *13*, 5540.
(13) Yuen, O. Y.; Leung, M. P.; So, C. M.; Sun, R. W.-Y.; Kwong, F. Y. Palladium-Catalyzed Direct Arylation of Polyfluoroarenes for Accessing Tetra-*ortho*-Substituted Biaryls: Buchwald-type Ligand Having Complementary -PPh_2 Moiety Exhibits Better Efficiency. *J. Org. Chem.* **2018**, *83*, 9008.

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX