ORGANOMETALLICS

pubs.acs.org/Organometallics Article

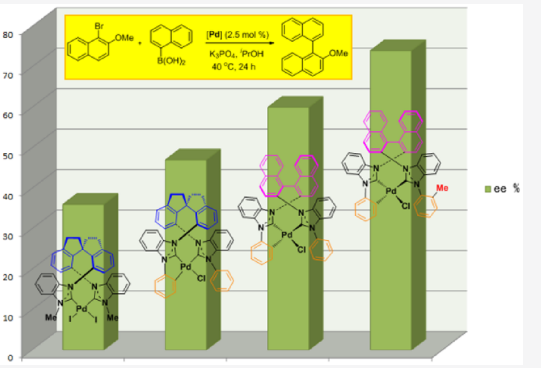
Fine Tuning of Chiral Bis(N-heterocyclic carbene) Palladium Catalysts for Asymmetric Suzuki−Miyaura Cross-Coupling Reactions: Exploring the Ligand Modification

Dao Zhang* and Jueqin Yu

Cite This: https://dx.doi.org/10.1021/acs.organomet.0c00036 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Novel chiral *N*,*N*′-bisaryl bis(NHC) ligand precursors H_2[(*S*)-**2**]Cl_2 on a spiro scaffold and H_2[(*S*)-**3b−g**]Cl_2 with a binaphthyl linkage were rationally designed and their cyclometalated cis-chelated NHC palladium complexes (*S*)-**5**, (*S*)-**6**, and (*S*)-**7b−g** have been synthesized and fully characterized. Complexes **6** and **7b** were further confirmed by X-ray single-crystal analysis. Both complexes adopted a slightly distorted square planar geometry around the Pd(II) center. The structure of **6** consists of a rare dimeric arrangement incorporating two palladium(II) centers bonded through a short metal−metal bond (2.853(2) Å), indicating a Pd^{II}−Pd^{II} intramolecular interaction (<3.00 Å). These *N*,*N*′-bisaryl-bis(NHC)-Pd complexes together with *N*,*N*′-bisalkyl analogues {[(*S*)-**1a−d**]PdX_2} (X = I, (*S*)-**4a**; X = Br, (*S*)-**4b−d**) have been used in the asymmetric aryl−aryl cross-coupling reactions of arylboronic acids and aryl halides. The enantioselectivity of the biaryl products was greatly improved within 24 h (up to 74% ee) when complexes **7a−g** were used as catalysts. The results show that for these types of bis(NHC) palladium catalysts the structural characters of the chiral scaffolds play a decisive role in the enantioselectivities of cross-coupling reactions.



INTRODUCTION

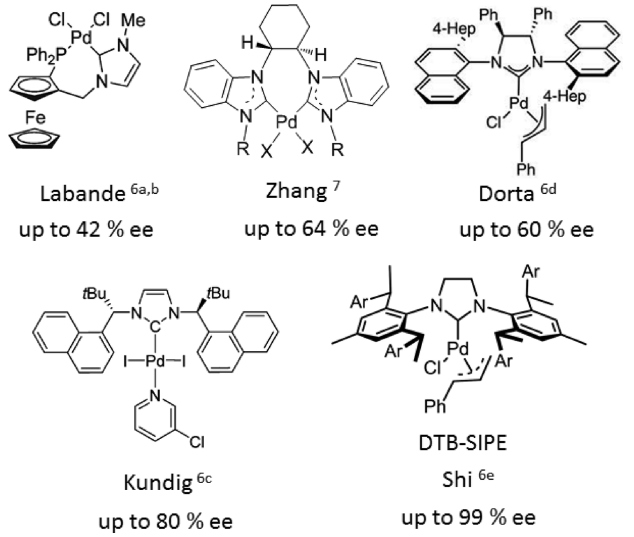
To date, the Pd-catalyzed asymmetric Suzuki−Miyaura cross-coupling reaction has been recognized as one of the most practical methods to construct the axially chiral biaryl skeletons that are common in a wide variety of natural products and drugs.[1] The most important problem in this realm is the design and synthesis of effective chiral ligands, because they control the spatial structure of the catalytic active center.[2] Pioneered by the groups of Buchwald and Cammidge in 2000,[2] an array of chiral auxiliary ligands such as (*S*)-KenPhos, (*S*,*S*,*S*,*S*)-bis-hydrazone, (*R*)-BI-DIME, (*R*,*R*,*R*,*R*)-DTB-SIPE, etc. has been developed.[3−7] Both experimental results and theoretical calculations have shown that a favorable chiral ligand is the key to the excellent enantioselectivity of highly efficient metal catalysts. Accordingly, the search for new chiral ligands for the broadest possible substrate scope is still a fundamental strategy for constructing atropisomers.

As a kind of highly strongly donating ligand, N-heterocyclic carbenes (NHCs) usually form a palladium catalyst robust to air and moisture, which would be beneficial for the oxidative addition of aryl halides and tolerance to the coupling partners with various coordination atoms.[8] In comparison to the broad study and application of chiral P-containing ligands in enantioselective cross-coupling catalysis, much less attention has been paid to chiral NHC ligands/catalysts.[9] Since the pioneering study disclosed by Labande et al. in 2010,[6a] several types of chiral monodentate NHC[6c−e] and NHC-containing chelating ligands[6b,7] have been developed in Pd-catalyzed asymmetric Suzuki−Miyaura cross coupling reactions (Scheme 1). Among these, the ligand (*R*,*R*,*R*,*R*)-DTB-SIPE is undoubtedly the first highly enantioselective (>90% ee) example that effectively suppresses the rotation around the metal−carbon(NHC) bond with its C_2-symmetric bulky aryl substituents on the nitrogen positions of the NHC skeleton.[6e]

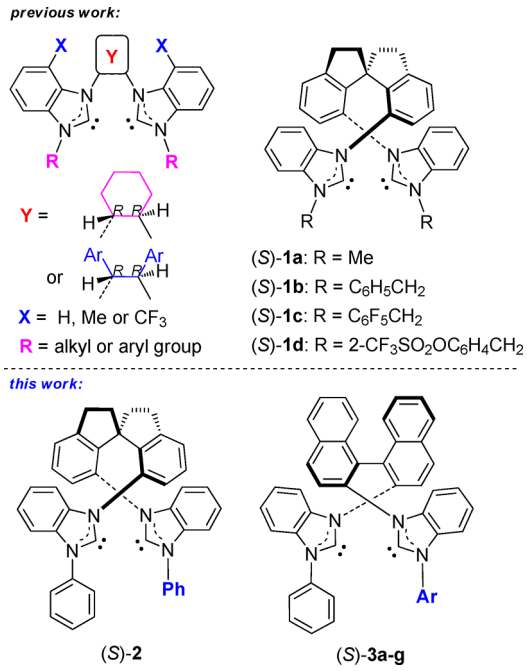
During our investigation on chiral NHC ligands for metal-catalyzed asymmetric C(sp^2)−C(sp^2) cross-coupling reactions, several types of bis(NHC) chelating ligands with different chiral linkers (Scheme 2) have been designed, although the best enantioselectity obtained was 64% ee.[7] To further study the influence of the chiral linker on the catalytic behavior, we recently prepared the *N*,*N*′-bisalkyl-substituted bis(NHC) ligands (*S*)-**1a−d** (Scheme 2) on a chiral spiro scaffold.[10] Although their palladium complexes achieved moderate to excellent ee values in enantioselective oxidative kinetic resolution of secondary alcohols, biaryl atropisomers with up

Received: January 17, 2020

Scheme 1. Examples of Chiral NHC Ligands in Asymmetric Suzuki−Miyaura Reactions



Scheme 2. Bis(NHC) Ligands with a Chiral Linker



to 36% ee could be obtained for Pd-catalyzed Suzuki−Miyaura cross-coupling reactions (see below). Later we synthesized the *N,N′*-bisaryl-substituted bis(NHC) ligand (*S*)-**2** with a spiro linker (Scheme 3), together with its analogue (*S*)-**3a** with an axially chiral binaphthyl linker[11] (Scheme 4). The catalytic experiments showed that the palladium complex of (*S*)-**3a** revealed a better catalytic enantioselectivity in comparison to that of (*S*)-**2** under the same reaction conditions. Later the structural fine-tuning of ligand (*S*)-**3a** was carried out to further improve the chiral surroundings around palladium centers ((*S*)-**3b−g**, Scheme 4). In the present contribution, we describe the synthesis, characterization, and catalytic behaviors of these chiral bis(NHC) palladium compounds.

RESULTS AND DISCUSSION

Synthesis and Characterization. The complexes {[(*S*)-**1a−d**]PdX_2} (X = I, (*S*)-**4a**; X = Br, (*S*)-**4b−d**) were prepared from *N,N′*-bisalkyl-substituted ligands H_2[(*S*)-**1a−d**]X_2 as we previously reported.[10] Complexes (*S*)-**5**, (*S*)-**6** and (*S*)-**7a−g** were synthesized from the tetraamine intermediates (*S*)-**8** and (*S*)-**10**, as shown in Schemes 3 and 4, respectively.

We first attempted to prepare the *N,N′*-bisaryl-substituted palladium complex (*S*)-**5** on a chiral spiro scaffold from $Pd_2(dba)_3$ in THF using a way similar to that for (*S*)-**7a** with a chiral BINAM linker.[11] Unfortunately, the yield of the desired complex was only ca. 10%. The worse outcome could be explained by the rigid spiro framework of (*S*)-**2**. In the ^{1}H NMR spectra of (*S*)-**5**, the singlet centered at 9.99 ppm representing its NCHN group of H_2[(*S*)-**2**]Cl_2 was notably absent. The two resonances in low-field region (180.7 and 197.4 ppm, respectively) in its ^{13}C NMR spectrum were very close to those (180.4 and 197.5 ppm) of (*S*)-**7a**, which indicated they should have structures similar to each other.

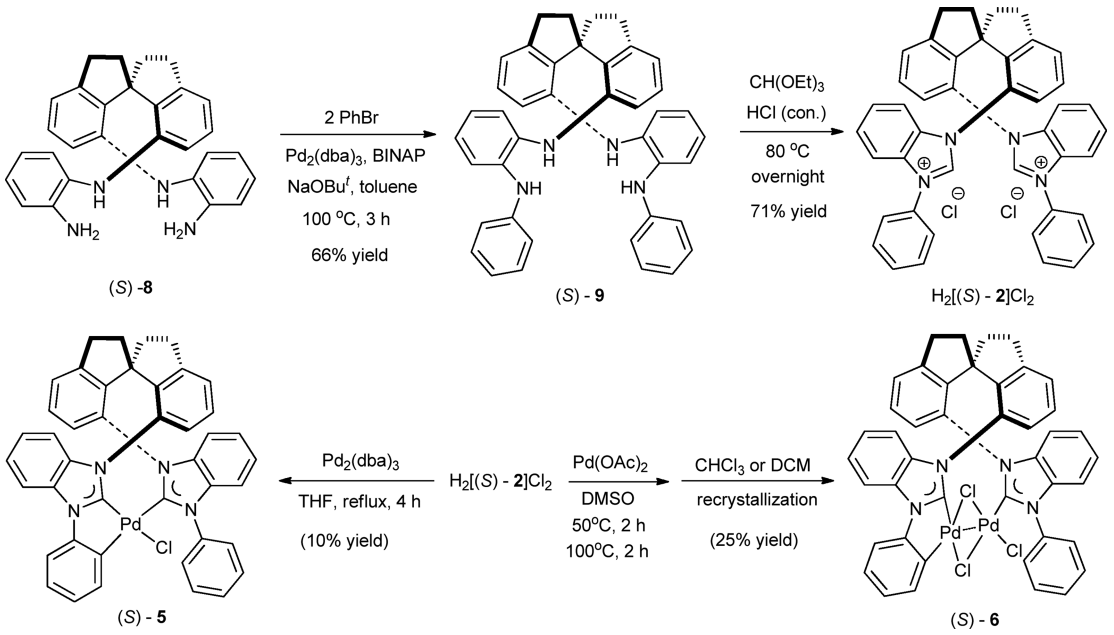
Given that the above strategy was inefficient in the construction of the chiral bis(NHC) complex, we next undertook a typical synthetic method using $Pd(OAc)_2$ as the starting material.[7] A mixture of precursor H_2[(*S*)-**2**]Cl_2 and an equivalent amount of $Pd(OAc)_2$ in DMSO was heated and kept at 50 °C for 2 h and 100 °C for 2 h, respectively, to give a mixture of (*S*)-**6** (major) and (*S*)-**5** (minor) according to the ^{13}C NMR spectrum in ca. 25% yield. Fortunately, the pure complex (*S*)-**6** could be obtained as orange bulk crystals by slowly evaporating its chloroform solution over several weeks. It is worth noting that there is a great difference between the two NHC resonances (163.7, 178.6 ppm, respectively) in (*S*)-**6**, which showed that the two carbene carbons coordinating with palladium are more distinguishable.

The crystal structure of (*S*)-**6** was determined by X-ray crystallography, and the ORTEP drawing is depicted in Figure 1. The structure of (*S*)-**6** consists of a rare dimeric arrangement incorporating two palladium(II) centers bonded through two bridging chloride ligands. The distance (2.853(2) Å) between the two palladium atoms is close to the generally accepted value indicating a $Pd^{II}\cdots Pd^{II}$ interaction (<3.00 Å), consistent with the previously reported μ-bridged dimeric complexes $\{Pd^{II}\}_2$.[12] From its side view (Figure S1) it appears that the coordination geometry around each metal atom could be considered as a square-planar environment. The dihedral angle between the coordination planes of P−Pd1 (defined by C1, Cl3, Cl1, Cl2) and P−Pd2 (defined by C25, C33, Cl2, Cl1) is 79.61°. The $C1_{NHC}$ ring is inclined to P−Pd1 at an angle of 75.60°, while the $C25_{NHC}$ ring is approximately parallel to P−Pd2 (9.94°). The Pd−$C_{carbene}$ (1.91(2) −1.967(19) Å) and Pd−Cl bond distances (2.312(6)−2.472(5) Å) are within the normal range.[6,7]

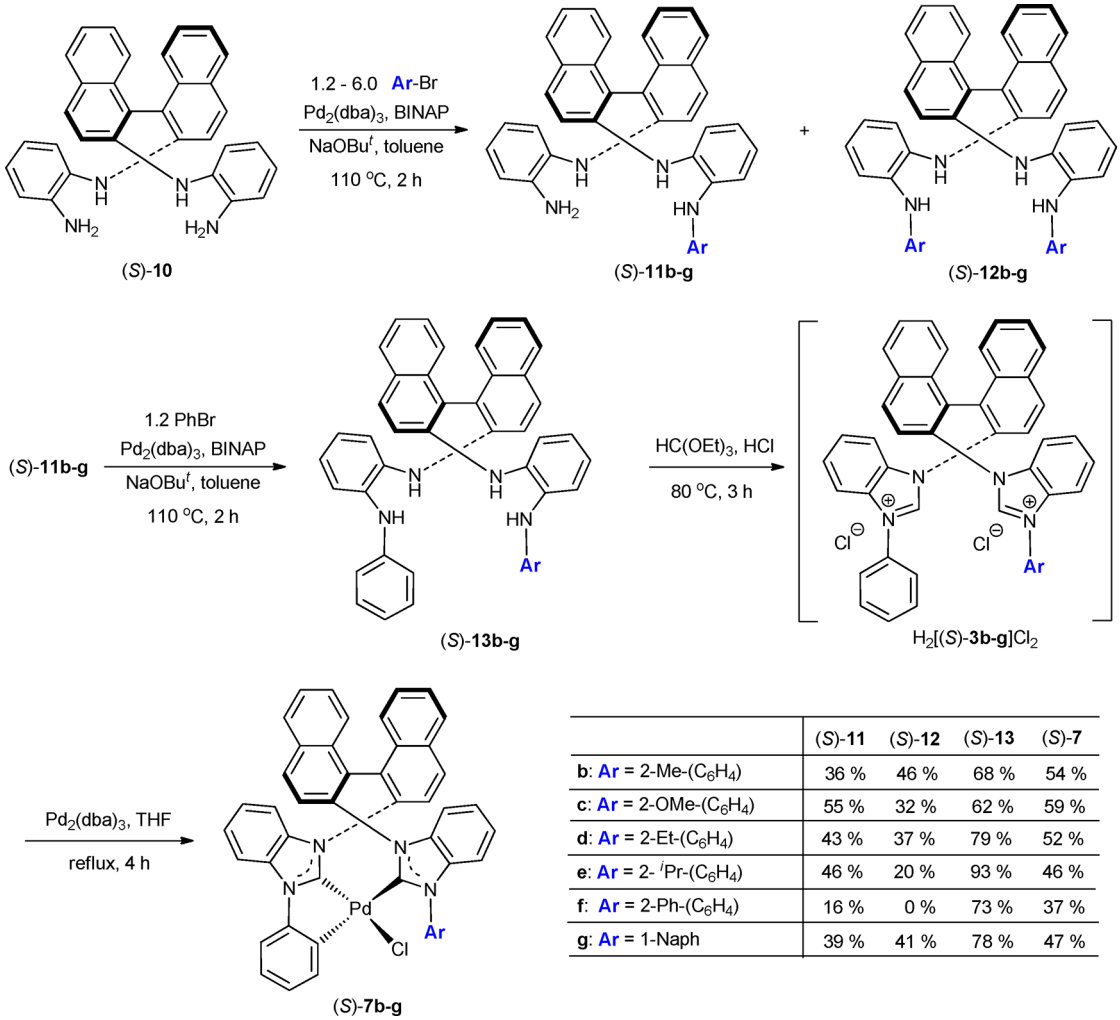
Considering that complexes (*S*)-**7b−g** contain two different aryl groups on the nitrogen positions of the NHC ligands, we planned to carry out the Pd-catalyzed C−N coupling reactions of (*S*)-**10** twice on the bais of the principle of "difficult first, easy later". From data summarized in Scheme 4, it would seem that the isolated yields of the intermediates (*S*)-**11b−g** is mainly related to the electronic effects and steric effects of substitute groups (ArBr). Previously Shi et al. prepared the disubstituted compound (*S*)-**12a** from the BINAM derivative (*S*)-**10** using 5.7 equiv of bromobenzene in 90% yield. In order to get the more monosubstituted compound (*S*)-**11**, we

https://dx.doi.org/10.1021/acs.organomet.0c00036
Organometallics XXXX, XXX, XXX−XXX

Scheme 3. Synthesis of Complexes (*S*)-5 and (*S*)-6



Scheme 4. Synthesis of Complexes (*S*)-7b–g



	(*S*)-**11**	(*S*)-**12**	(*S*)-**13**	(*S*)-**7**
b: Ar = 2-Me-(C_6H_4)	36 %	46 %	68 %	54 %
c: Ar = 2-OMe-(C_6H_4)	55 %	32 %	62 %	59 %
d: Ar = 2-Et-(C_6H_4)	43 %	37 %	79 %	52 %
e: Ar = 2-^{i}Pr-(C_6H_4)	46 %	20 %	93 %	46 %
f: Ar = 2-Ph-(C_6H_4)	16 %	0 %	73 %	37 %
g: Ar = 1-Naph	39 %	41 %	78 %	47 %

https://dx.doi.org/10.1021/acs.organomet.0c00036
Organometallics XXXX, XXX, XXX−XXX

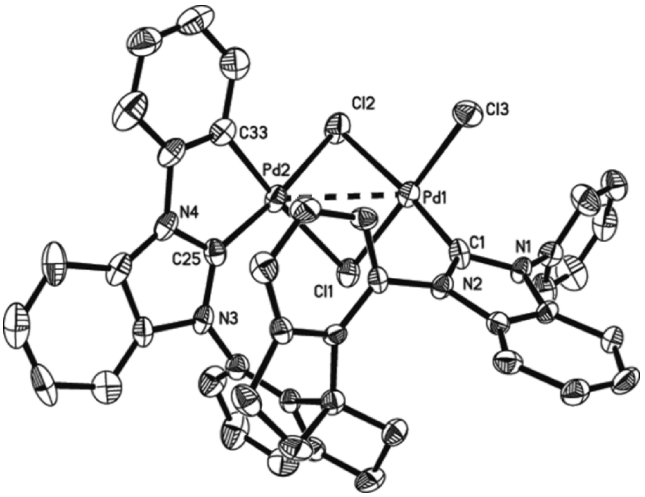


Figure 1. Molecular structure of (*S*)-**6** (H atoms omitted for clarity). Selected bond lengths (Å) and angles (deg): Pd1−C1 1.91(2), Pd1−Cl1 2.328(6), Pd1−Cl2 2.405(5), Pd1−Cl3 2.312(6), Pd2−Cl1 2.472(5), Pd2−Cl2 2.403(6), Pd2−C25 1.967(19), Pd2−C33 2.03(2), Pd1···Pd2 2.853(2), C1−Pd1−Cl3 87.1(6), C1−Pd111−Cl1 90.5(6), Cl3−Pd1−Cl1 173.8(2), C1−Pd1−Cl2 172.6(5), Cl3−Pd1−Cl2 96.0(2), Cl1−Pd1−Cl2 85.6(2), C1−Pd1−Pd2 119.1(5), Cl3−Pd1−Pd2 120.63(17), Cl1−Pd1−Pd2 55.88(13), Cl2−Pd1−Pd2 53.57(14), C25−Pd2−C33 77.8(9), C25−Pd2−Cl2 173.6(6), C33−Pd2−Cl2 96.3(7), C25−Pd2−Cl1 103.6(6), C33−Pd2−Cl1 171.5(6), Cl2−Pd2−Cl1 82.6(2), Pd1−Cl1−Pd2 72.88(17), Pd2−Cl2−Pd1 72.80(15).

decided to reduce the amount of aryl halides. After many tries, the reaction of (*S*)-**10** with 1.2 equiv of ArBr gave better yields for (*S*)-**11b−e,g** (36−55%) along with (*S*)-**12b−e,g** (20−46%). It should be noted, however, that for (*S*)-**11f** with s more bulky substituent a large excess (at least 6.0 equiv) of aryl bromide was necessary together with a long reaction time, although the yield still was very low (16%). Moreover, compound (*S*)-**11c** with a 2-OMe-C_6H_4 group achieved the highest yield of 55% and we tried but failed to obtain similar analogues with an electron-withdrawing group such as 2-CF_3-C_6H_4. Compounds (*S*)-**13b−g** were obtained by a second N-arylation reaction of (*S*)-**11** with PhBr in good yields of 62−93%.

According to an improved literature method for (S)-**7a**,[11] (*S*)-**13b−g** underwent cyclization to produce the corresponding bis(NHC) precursors H_2[(*S*)-**3b−g**]Cl_2 in very favorable yields using excess triethyl orthoformate and concentrated HCl. Treatment of the above bis(benzimidazolium) salts with 1.2 equiv of $Pd_2(dba)_3$ in anhydrous THF under reflux for 4 h afforded the desired NHC metal complexes (*S*)-**7b−g** in moderate yields (37−59%).

All palladium NHC complexes were characterized by ^{1}H and ^{13}C NMR, and selected ^{13}C NMR data of C_{NHC} and $C_{2\text{-}R}$(Ar) are presented in Table 1. It is worth noting that two sets of resonances in the low-field region (198.9−179.9 ppm) in their ^{13}C NMR spectra showed that these NHC complexes had the two isomers (*S*)-**7b−g** and (*S*)-**7b′−g′** (Figure 2) and could not easily be separated from each other by gel chromatography. In general, the molar ratio of the major (*S*)-**7b−g** to the minor (*S*)-**7b′−g′** increased steadily with an increase in the steric hindrance of the substituent R in the ortho position of the phenyl ring (Figure S2).

Table 1. Selected ^{13}C Data (ppm) of Palladium Complexes (*S*)-7a−g

	$C_{carbene}$−Pd		$C_{2\text{-}R}$(Ar)	
complex (Ar)	major	minor	major	minor
(*S*)-**7a** (Ph)	197.5, 180.4			
(*S*)-**7b**/**7b′** (2-Me-C_6H_4)	198.4, 180.7	197.7, 180.3	19.3	18.7
(*S*)-**7c**/**7c′** (2-OMe-C_6H_4)	197.2, 180.9	198.1, 179.9	56.2	55.2
(*S*)-**7d**/**7d′** (2-Et-C_6H_4)	197.7, 180.2	198.3, 180.6	13.9, 23.5	13.0, 23.7
(*S*)-**7e**/**7e′** (2-^{i}Pr-C_6H_4)	197.7, 180.2	180.4	22.9, 24.7, 27.1	24.3, 25.7, 28.1
(*S*)-**7f** (2-Ph-C_6H_4)	197.5, 180.5			
(*S*)-**7g**/**7g′** (1-Naph)	198.6, 180.0	198.9, 180.9		

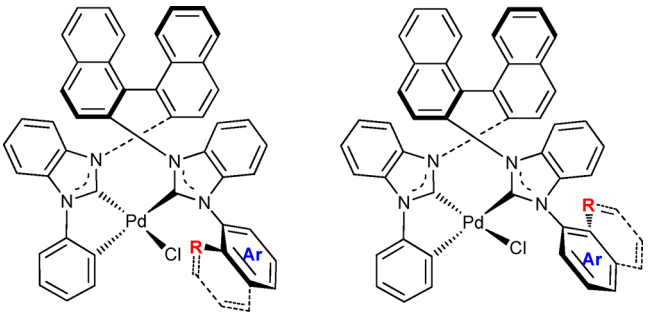


Figure 2. Two isomeric complexes (*S*)-7 and (*S*)-7′.

Sometimes the signal of the minor product, such as (*S*)-**7f′** with a phenyl group, was so weak that it was very difficult to use NMR techniques to observe it. Of course, on the basis of the values of chemical shifts and integral areas in ^{1}H NMR spectra, the molar ratio (*S*)-7/(*S*)-7′ could also be easily estimated. For example, the value of (*S*)-**7c**/(*S*)-**7c′** is 1.00/0.55 on the basis of OCH_3 centered at 2.82 and 3.57 ppm, while that of (*S*)-**7e** and (*S*)-**7e′** is 1.00/0.21 according to CH_{iPr} centered at 2.19 and 2.94 ppm.

A suitable single crystal of complex (*S*)-**7b**/(*S*)-**7b′** was successfully obtained by means of solvent diffusion (chloroform/hexane). The isomerism of these NHC palladium complexes was further confirmed by X-ray single-crystal diffraction analysis. There are two isomers ((*S*)-**7b**/(*S*)-**7b′**) in the unit cell (Figure 3), and an ORTEP drawing of (*S*)-**7b** is depicted in Figure 4. The methyl group and chloride ligand are located on the same side of the benzimidazole ring defined by N3−C34−N4−C35−C40 in (*S*)-**7b**, while they lie on opposite sides in (*S*)-**7b′**.

As shown in Figure 4, two carbene carbon atoms, one phenyl carbon atom, and one chloride coordinated with the palladium center and the cyclometalated complex adopted a square-planar geometry around the Pd(II) center. The two Pd−$C_{carbene}$ bond distances (1.983(8) and 2.008(8) Å) are almost equal to each other in *N*,*N*′-bisalkyl bis(NHC) complexes such as the [Pd((*S*)-**1a**)I_2] and [Pd((*S*)-**1b**)Br_2] we previously reported.[10] However, there are clear and obvious differences between them in the *N*,*N*′-bisaryl bis(NHC) palladium complex(*S*)-**7b** (1.978(9) and 2.042(8) Å) due to the C−H activation of the neighboring phenyl group. The difference in

https://dx.doi.org/10.1021/acs.organomet.0c00036
Organometallics XXXX, XXX, XXX−XXX

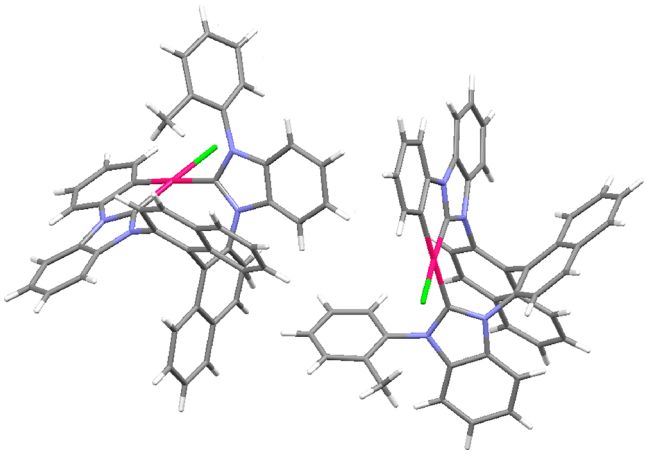


Figure 3. Isomers (*S*)-**7b** (right) and (*S*)-**7b′** (left) in a unit cell.

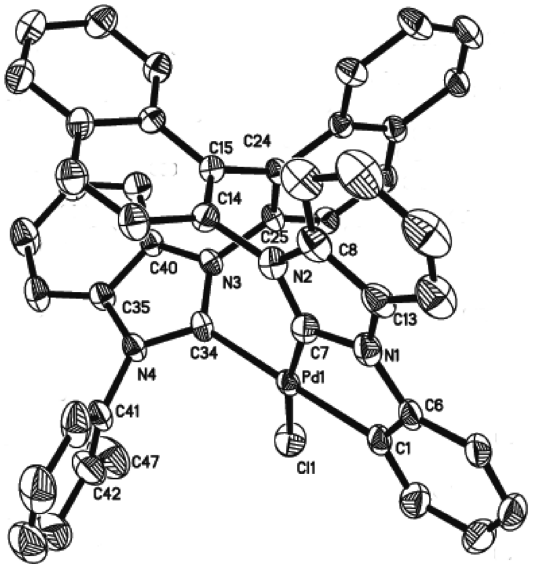


Figure 4. Molecular structure of (*S*)-**7b** (H atoms omitted for clarity). Selected bond lengths (Å) and angles (deg): Pd1−C1 2.028(8), Pd1−C7 1.978(9), Pd1−C34 2.042(8), Pd1−Cl1 2.350(2), C7−Pd1−C1 78.8(4), C7−Pd1−C34 101.4(3), C1−Pd1−C34 178.6(3), C7−Pd1−Cl1 170.5(2), C1−Pd1−Cl1 94.5(3), C34−Pd1−Cl1 85.1(2).

bond length is more noticeable in (*S*)-**7a** (1.927(6) and 2.055(6) Å)[11] because the ligand (*S*)-**3a** has a smaller hindrance in comparison to (*S*)-**3b−g**. Moreover, the Pd−C_{Ph} (2.028(8) Å) and Pd−Cl bond distances (2.350(2) Å) were slightly longer than those (2.016(6), 2.3364(19) Å) in (*S*)-**7a**. The complex (*S*)-**7b** (101.4(3)°) has a $C_{carbene}$−Pd−$C_{carbene}$ bite angle similar to that (*S*)-**7a** (102.3(2)°), which are much bigger than that in an analogue (94.8(3)°) with a spiro linker.[10]

Asymmetric Suzuki−Miyaura Coupling. The N-alkyl substituted palladium complex (*S*)-**4a** and the N-aryl-substituted analogue (*S*)-**5** on a spiro scaffold were initially tested in the asymmetric Suzuki−Miyaura cross-coupling reaction between 1-bromo-2-methoxynaphthalene (**14a**) and naphthylboronic acid (**15a**). As shown in Table 2 (entries 1−8 and entries 15−20), ^{i}PrOH and K_3PO_4 proved to be the best solvent and base, respectively. Under the optimum conditions the ee % value of the axially chiral biaryl **16** can get up to 36% ((*S*)-**4a**) and 47% ((*S*)-**5**) (entries 8 and 17). Both the conversation and enantioselectivity of the Suzuki−Miyaura reaction markedly decrease with an increase in steric hindrance from alkyl groups on the nitrogen positions of bis(NHC) in complexes (*S*)-**4b−d** (entries 9−11 vs entry 8). For (*S*)-**4a**, when aryl halide **14a** (R^2 = OMe) was displaced by **14b** (R^2 = OBn) or **14c** (R^2 = Me) their conversion ratios changed significantly with a slightly reduced enantioselectivity (entries 12 and 13 vs entry 8). Moreover, the aryl boronic acids **15a−d** do suffer significant side reactions to afford homocoupling and deboronation byproducts (**17a,b** and **19a,b**), especially for those bulky partners. For example, the cross-coupling reaction of 2-methoxynaphthylboronic acid (**15b**) with 1-bromonaphthalene (**14d**) afforded not the desired biaryl product (**16db**) but 2-methoxynaphthalene (**19b**) in about 60% isolated yield based on **15b**, together with a small amount of the debromination byproduct (**18d**) of the aryl halide **14d** (entry 14).

Next we investigated the catalytic behaviors of axially chiral bis(NHC) palladium complexes (*S*)-**7a−g** that have a structure similar to that of (*S*)-**5** on a spiro scaffold. The preliminary experiments were performed in isopropyl alcohol at 40 °C, using K_3PO_4 as the base, an excess (1.5 equiv) of **15a**, and 2.5 mol % of complexes (*S*)-**7a−g** as the catalyst (Table 3). We were delighted to observe that the desired product **16aa** was obtained with significant ee values in most cases, reaching a promising 74% ee when (*S*)-**7b** was used as a catalyst (entries 1−5). Meanwhile, the molar ratio of the desired product **16aa** to the homocoupling counterpart 1,1′-binaphthyl (**17**) also reaches a maximum of 2.2 (entry 2). Moreover, complexes (*S*)-**7f** and (*S*)-**7g** could afforded only a trace of biaryl product **16** (entries 6 and 7).

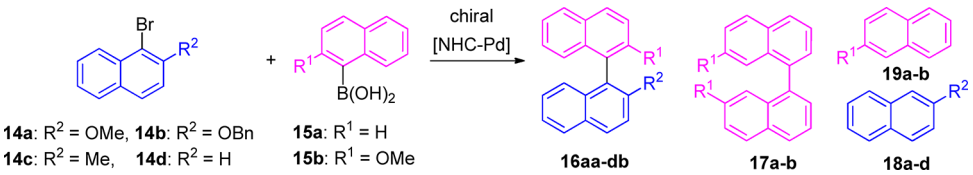
A typical substrate scope screening test of the Suzuki−Miyaura reaction with (*S*)-**7b** as the catalyst was performed. Under the representative conditions (entry 2, Table 4), several naphthyl halides **14a-e** and arylboronic acids **15a-f** with different steric substituents were investigated for coupling with each other (Table 4). It is a great pity that we did not observe an obvious improvement in coupling enantioselectivity (from 21% to 69%), albeit with relatively higher conversions (from 50% to 71%) in some cases (entries 1, 2, and 5). Moreover, we failed to obtain the tetra-ortho-substituted biaryl products by Suzuki coupling using these palladium catalysts (entry 7, Table 4).

CONCLUSIONS

In conclusion, a variety of novel *N*,*N*′-bisaryl-substituted chiral bis(NHC) ligand precursors on a spiro or axial bisaryl scaffold and their palladium complexes have been prepared in good yields and characterized by NMR, HRMS, elemental analysis ,and X-ray single-crystal diffraction. The obtained bis(NHC)−Pd complexes (*S*)-**7a−g** with an axial chiral linkage proved to be more efficient catalysts (up to 74% ee) in comparison to those on a spiro scaffold (up to 47% ee) for asymmetric Suzuki−Miyaura reactions of arylboronic acids and aryl halides. Further fine tuning using different groups on the cis positions of nitrogen seemed to have little effect on the enantioselectivities (from 60% to 74% ee) of the axially chiral biaryl products. At the same time, one side effect is that bulky substituents usually decrease the chemical reaction rate, causing low yield/conversion. The results show that for these types of bis(NHC) palladium catalysts the structural characters of the chiral scaffolds play a decisive role in the

https://dx.doi.org/10.1021/acs.organomet.0c00036
Organometallics XXXX, XXX, XXX−XXX

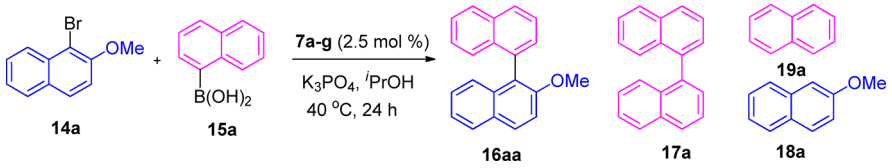
Table 2. Asymmetric Suzuki–Miyaura Coupling Reactions Using (*S*)-4a-d and (*S*)-5[a]



entry	cat. (mol %)	coupling partners	base	solvent	time (h)	*T* (°C)	conversn[b] (%)	sel[b] (%)	ee[c] (%)
1	**4a** (2)	**14a/15a**	Cs_2CO_3	toluene	24	80	5	92	*d*
2	**4a** (2)	**14a/15a**	K_3PO_4	toluene	24	80	30	95	3
3	**4a** (4)	**14a/15a**	K_3PO_4	toluene	24	80	32	97	7
4	**4a** (2)	**14a/15a**	K_3PO_4	toluene	48	80	55	97	1
5	**4a** (2)	**14a/15a**	K_3PO_4	toluene	96	80	31	97	*d*
6	**4a** (2)	**14a/15a**	K_3PO_4	^{i}PrOH	48	80	88	85	2
7	**4a** (2)	**14a/15a**	K_3PO_4	^{i}PrOH	48	60	50	95	24
8	**4a** (2)	**14a/15a**	K_3PO_4	^{i}PrOH	120	40	82	93	36
9	**4b** (2)	**14a/15a**	K_3PO_4	^{i}PrOH	120	40	77	59	21
10	**4c** (2)	**14a/15a**	K_3PO_4	^{i}PrOH	120	40	37	94	5
11	**4d** (2)	**14a/15a**	K_3PO_4	^{i}PrOH	120	40	58	94	31
12	**4a** (2)	**14b/15a**	K_3PO_4	^{i}PrOH	120	40	82	95	33
13	**4a** (2)	**14c/15a**	K_3PO_4	^{i}PrOH	120	40	81	84	31
14	**4a** (2)	**14d/15b**	K_3PO_4	^{i}PrOH	120	40	*e*, *f*		
15	**5** (3)	**14a/15a**	K^{t}OBu	^{i}PrOH	24	40	18	21	7
16	**5** (3)	**14a/15a**	K^{t}OBu	^{i}PrOH	72	40	11	24	2
17	**5** (3)	**14a/15a**	K_3PO_4	^{i}PrOH	24	40	36	83	47
18	**5** (3)	**14a/15a**	K_2CO_3	^{i}PrOH	24	40	5	>90	*d*
19	**5** (3)	**14a/15a**	K_3PO_4	toluene	24	40	3	38	*d*
20	**5** (3)	**14a/15a**	K_3PO_4	MeOH	24	40	trace		

[a]Reaction conditions: 0.2 mmol of aryl bromides **14a–d**, 0.3 mmol of aryl boronic acids **15a,b**, 0.5 mmol of base, 2 mL of solvent. [b]Determined by GC-MS: conversn (%) = {[**16** + **18**]/**14**} × 100%; sel (%) = {**16**/[**16** + **18**]} × 100%. [c]Determined by HPLC equipped with a Chiralcel IA column. [d]Not determined due to the low conversion. [e]No desired biaryl peoduct. [f]By GC analysis, there are 1-bromonaphthalene (53%), 2-methoxynaphthalene (43%), and naphthalene (3%) in the reaction mixture.

Table 3. Asymmetric Suzuki–Miyaura Coupling Reactions Using Catalysts (*S*)-7a–g[a]



entry	cat.	conversn[b] (%)	sel[b] (%)	ee[c] (%)	confign[d]	**16aa**/**17**[b]
1	**7a**	43	89	60	*R*	1.0
2	**7b**	32	96	74	*R*	2.2
3	**7c**	25	39	50	*R*	0.3
4	**7d**	26	29	60	*R*	0.5
5	**7e**	17	28	70	*R*	0.5
6	**7f**	9	10	*e*		
7	**7g**	trace				

[a]Reaction conditions: 0.2 mmol of **14a**, 0.3 mmol of **15a**, 0.5 mmol of K_3PO_4, 2 mL of ^{i}PrOH. [b]Based on aryl bromide **14a** and determined by GC-MS. [c]Determined by chiral HPLC equipped with a Chiralcel IA column. [d]Configurations of biaryls were assigned according to the literature[13] (the *S* isomer should come before the *R* isomer). [e]Not determined.

enantioselectivities of aryl–aryl cross-coupling reactions. Efforts to develop a perfect chiral fragment with strong enantioselectivity from a large amount of chiral elements in the chiral pool are ongoing.

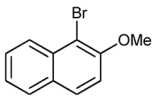
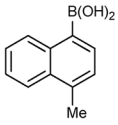
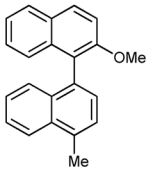
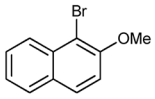
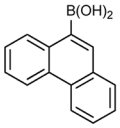
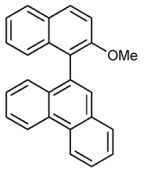
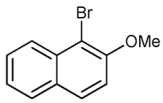
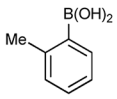
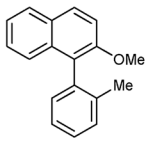
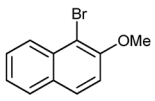
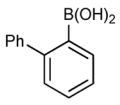
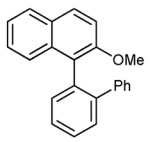
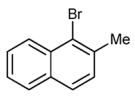
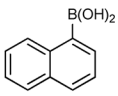
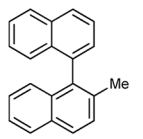
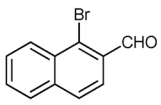
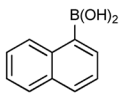
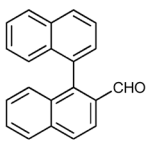
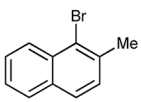
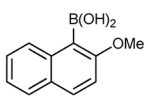
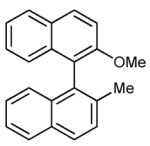
EXPERIMENTAL SECTION

General Specifications. All manipulations, unless stated otherwise, were performed using Schlenk or glovebox techniques under a dry argon atmosphere. Solvents were dried with standard methods and freshly distilled prior to use if needed. All chemicals unless noted otherwise were purchased from major commercial suppliers and used without purification. Ligands H_2[(*S*)-**1a–d**]X_2 (X = I, Br) and H_2[(*S*)-**3a**]Cl_2, and their palladium complexes (*S*)-**4a–d** and (*S*)-**7a** together with the intermediates (*S*)-**8**, (*S*)-**10**, and (*S*)-**12a** were prepared according to the literature methods.[10,11]

Instrumentation. NMR spectra were measured on JEOL ECA-400 spectrometers using TMS as an internal standard. Elemental and high-resolution mass spectral (HRMS) analyses were performed by the Analysis Center, Fudan University. Flash column chromatography

https://dx.doi.org/10.1021/acs.organomet.0c00036
Organometallics XXXX, XXX, XXX–XXX

Table 4. Typical Substrate Scope of Suzuki−Miyaura Cross-Coupling Using (*S*)-7b[a]

entry	Ar^1-Br	Ar^2-$B(OH)_2$	Ar^1-Ar^2	conv.[b] (%)	sel.[b] (%)	ee[c] (%)	ratio of **16**/**17**[b]
1	 **(14a)**	 **(15c)**	 **(16ac)**	50	87	53	3.2
2	 **(14a)**	 **(15d)**	 **(16ad)**	59	92	61	30.9
3	 **(14a)**	 **(15e)**	 **(16ae)**	24	81	69	1.2
4	 **(14a)**	 **(15f)**	 **(16af)**	2	10	d	1.0
5	 **(14c)**	 **(15a)**	 **(16ca)**	71	82	51[f]	2.0
6	 **(14e)**	 **(15a)**	 **(16ea)**	d.	d.	21[g]	d.
7	 **(14c)**	 **(15b)**	 **(16cb)**	e			

[a]Reaction conditions: 5 μmol of (*S*)-**7b**, 0.2 mmol of **14a,c,e**, 0.3 mmol of **15a−f**, 0.5 mmol of K_3PO_4, 2 mL of ^{i}PrOH. [b]Based on aryl bromides **14a,c,e** and determined by GC-MS. [c]Determined by chiral HPLC equipped with a Chiralcel IA column unless specified otherwise. [d]Not determined. [e]No desired biaryl peoduct. [f]With a Chiralcel OJ-H column. [g]With a Chiralcel IC column.

was carried out on silica gel (300−400 mesh). GC chromatograms were recorded on a HP 4890A GC instrument equipped with a DB-5 MS UI capillary column. Flash column chromatography was carried out on silica gel (300−400 mesh). Analytical HPLC was performed

https://dx.doi.org/10.1021/acs.organomet.0c00036
Organometallics XXXX, XXX, XXX−XXX

using an Agilent 1100 series chromatograph equipped with a Chiralcel IA, IC, or OJ-H column, and the products were identified by comparison with authentic samples.

X-ray Structure Determination Details. Single crystals suitable for X-ray crystallography were obtained by diffusion of hexane into concentrated chloroform solutions of (*S*)-**6** and (*S*)-**7b** at room temperature over several days. The data were collected on a Bruker APEX-II CCD system with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) at 293 K. The structure was solved using direct methods, while all non-hydrogen atoms were further refined with full-matrix least squares on F^2 obtained with the SHELXTL program package.[14] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were introduced in calculated positions with the displacement factors of the host carbon atoms. The CCDC files 1978451 and 1978452 contain the crystallographic data for this paper.

Crystal data for (S)-6·CHCl$_3$: $C_{44}H_{32}Cl_6N_4Pd_2$, M_r = 1042.23, orange block, 0.220 × 0.110 × 0.060 mm, monoclinic, space group $P2_1$, a = 11.7521(8) Å, b = 19.9880(13) Å, c = 17.5819(11) Å, α = 90°, β = 90.445(2)°, γ = 90°, V = 4122.5(5) Å^3, Z = 4, ρ_{calcd} = 1.679 g cm^{-3}, μ = 7.361 mm^{-1}, F(000) = 2072, T = 296(2) K; all data, R1 = 0.0905 and wR2 = 0.2606; $I > 2\sigma(I)$, R1 = 0.0883 and wR2 = 0.2578; GOF 1.053, 16576 independent reflections ($2.19 \le 2\theta \le 56.998°$), 1009 parameters, 38 restraints.

Crystal data for (S)-7b: $C_{47}H_{31}ClN_4Pd$, M_r = 793.61, colorless sheet, 0.420 × 0.120 × 0.040 mm, triclinic, space group $P1$, a = 10.5969(9) Å, b = 12.0850(10) Å, c = 18.3811(16) Å, α = 97.416(2)°, β = 105.557(3)°, γ = 108.022(3)°, V = 2097.9(3) Å^3, Z = 2, ρ_{calcd} = 1.256 g cm^{-3}, μ = 2.981 mm^{-1}, F(000) = 808, T = 173(2) K; all data, R1 = 0.0615 and wR2 = 0.1772; $I > 2\sigma(I)$, R1 = 0.0603 and wR2 = 0.1757; GOF 1.058, 17103 independent reflections ($3.439 \le 2\theta \le 59.468°$), 1066 parameters, 269 restraints.

Synthesis of (*S*)-*N*^{1},*N*$^{1'}$-(2,2′,3,3′-Tetrahydro-1,1′-spirobi[indene]-7,7′-diyl)bis(*N*^{2}-phenylbenzene-1,2-diamine) ((*S*)-9). Under an argon atmosphere, a mixture of (*S*)-*N*^{1},*N*$^{1'}$-(2,2′,3,3′-tetrahydro-1,1′-spirobi[indene]-7,7′-diyl)bis(benzene-1,2-diamine) ((*S*)-**8**; 388 mg, 0.9 mmol), bromobenzene (0.30 mL, 2.8 mmol), $Pd_2(dba)_3$ (24 mg, 0.002 mmol), BINAP (50 mg, 0.08 mmol), and NaOBu^t (0.35 g, 3.6 mmol) were stirred in anhydrous toluene (14 mL) at 100 °C for 3 h. The reaction mixture was cooled to room temperature, and water was added to quench the reaction. The insoluble materials of the mixture were removed by filtration. The organic compound was extracted with Et_2O (30 mL), washed with H_2O (25 mL × 3) and brine (25 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by silica gel flash column chromatography (PE/DCM = 2/1, R_f = 0.55) to give (*S*)-**9** as a red solid. Yield: 387.2 mg (66%). Anal. Calcd for $C_{41}H_{36}N_4$ (M = 584.75 g mol^{-1}): C, 84.21; H, 6.21; N, 9.58. Found: C, 84.10; H, 6.27; N, 9.76. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16−2.32 (m, 4H), 2.88−2.94 (m, 2H), 3.00−3.08 (m, 2H), 5.00 (br s, 2H, HN), 5.48 (s, 2H, NH), 6.69−6.71 (m, 6H), 6.82−6.93 (m, 8H), 6.99 (d, J = 8.0 Hz, 2H), 7.13−7.18 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.2 (CH_2), 36.4 (CH_2), 59.2 (C), 113.2, 117.2, 118.0, 119.6, 120.3, 120.6, 122.5, 123.1, 129.0, 132.2, 133.7 (CH), 135.7, 140.8, 143.7, 145.3 (C). HRMS (positive ions): m/z calcd for $C_{41}H_{37}N_4$ $[M + H]^+$, 585.3018; found, 585.3024.

Synthesis of Chiral Bis(benzimidazolium) Salt H$_2$[(*S*)-2]Cl$_2$. In a round-bottomed flamed flask (25 mL) equipped with a rubber septum and magnetic stirbar were placed (*S*)-**9** (0. 321 g, 0.55 mmol) and $HC(OEt)_3$ (14.0 mL). Then, 12.1 N HCl (0.1 mL) was added dropwise using a syringe. The resulting suspension was stirred at room temperature for 30 min under argon and then heated to 80 °C until condensation was observed on the neck of the flask. At this point, the rubber septum was removed, and the solution was allowed to sit open to the air for 2 h. After the solution was cooled to room temperature, the supernatant was removed by decantation. The white solid obtained was washed several times with diethyl ether, followed by removal of residual solvents under high vacuum to afford H_2[(*S*)-**2**]Cl_2 as a yellow solid. Yield: 0.287 g (71%). Anal. Calcd for $C_{43}H_{34}Cl_2N_4$ (M = 677.66 g mol^{-1}): C, 76.21; H, 5.06; N, 8.27. Found: C, 76.13; H, 5.21; N, 8.38. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.11−2.17 (m, 2H), 2.36−2.43 (m, 4H), 2.95−3.02 (m, 2H), 7.08−7.11 (m, 4H), 7.39−7.41 (m, 4H), 7.63−7.67 (m, 3H), 7.71−7.81 (m, 7H), 9.99 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.7 (CH_2), 41.8 (CH_2), 60.6 (C), 113.3, 114.0, 124.1, 128.3, 128.8, 129.0, 129.1, 129.6, 130.2, 132.6, 133.3, 143.0, 146.4, 146.5. HRMS (positive ions): m/z calcd for $C_{43}H_{33}N_4$ $[M - 2Cl - H]^+$, 605.2694; calcd for $C_{43}H_{34}N_4$ $[M - 2Cl]^{2+}$, 303.1386; found, 605.2682, 303.1402.

Synthesis of Palladium Compound (*S*)-5. Under an argon atmosphere, a mixture of H_2[(*S*)-**2**]Cl_2 (183 mg, 0.27 mmol) and $Pd_2(dba)_3$ (293 mg, 0.32 mmol) was stirred in anhydrous THF (14 mL) under reflux for 4 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel to give (*S*)-**5** as a off-white solid. Yield: 0.020 g (10%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47−1.51 (m, 2H), 2.13−2.26 (m, 4H), 2.62−2.70 (m, 2H), 6.82−7.20 (m, 10H), 7.28−7.33 (m, 4H), 7.82 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7, 30.2 (CH_2), 39.2, 41.7 (CH_2), 60.9 (C), 111.3, 111.9, 112.6, 122.9, 123.1, 123.5, 124.1, 124.6, 124.7, 125.6, 126.6, 127.8, 128.3, 128.5, 128.8, 129.1, 129.7, 130.5, 133.2, 134.4, 134.7, 135.7, 137.0, 137.1, 137.5, 141.9, 143.4, 146.6, 147.6, 147.8, 150.2 (Ar), 180.7, 197.4 (C−Pd). HRMS (positive ions): m/z calcd for $C_{43}H_{31}N_4Pd$ $[M - Cl]^+$, 709.1584; found, 709.1580. Anal. Calcd for $C_{43}H_{31}ClN_4Pd$ (M = 745.6060 g mol^{-1}): C, 69.27; H, 4.19; N, 7.51. Found: C, 69.38; H, 4.24; N, 7.47. Moreover, the unreacted ligand H_2[(*S*)-**2**]Cl_2 could be easily recycled by increasing the polarity of the eluent (EA/MeOH, 1/1). Yield: 0.065 g (40%).

Synthesis of Palladium Complex (*S*)-6. Under an argon atmosphere, a mixture of H_2[(*S*)-**2**]Cl_2 (53 mg, 0.078 mmol) and $Pd(OAc)_2$ (17.5 mg, 44.8 mg, 0.078 mmol) in DMSO (2.0 mL) was stirred at 50 °C for 2 h and then at 100 °C for 2 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (eluent dichloromethane/ethyl acetate, 2/1) to give a mixture of (*S*)-**6** (major) and (*S*)-**5** (minor) according to its ^{13}C NMR spectra. Yield: ca. 0.034 g (25%). The pure complex (*S*)-**6** could be obtained as orange bulk crystals by slowly evaporating its chloroform solution for several weeks. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23−1.32 (m, 1H), 1.44−1.52 (m, 1H), 1.99−2.07 (m, 1H), 2.23−2.31 (m, 2H), 2.37−2.48 (m, 2H), 2.56−2.61 (m, 1H), 6.85 (d, J = 6.8 Hz, 1H), 6.91 (t, J = 7.6 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 7.17−7.37 (m, 9H), 7.40−7.43 (m, 2H), 7.52−7.72 (m, 7H), 8.08 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.1, 30.9 (CH_2), 42.0, 43.7 (CH_2), 62.0 (C), 111.2, 111.8, 112.0, 112.2, 112.4, 123.5, 124.4, 124.5, 124.9, 125.2, 126.6, 126.7, 127.3, 128.8, 128.9, 129.2, 129.5, 129.6, 129.9, 133.2, 133.8, 134.5, 135.9, 136.1, 136.9, 137.1, 137.2, 140.5, 142.4, 145.5, 146.1, 147.0, 147.4 (Ar), 163.7, 178.6 (C−Pd). Anal. Calcd for $C_{44}H_{32}Cl_6N_4Pd_2$ (M = 1042.3097 g mol^{-1}): C, 50.70; H, 3.09; N, 5.38. Found: C, 50.58; H, 3.15; N, 5.49.

Synthesis of Intermediates (*S*)-11b−g and (*S*)-12b−g. Under an argon atmosphere, a mixture of BINAM-tetraamine (*S*)-**10** (200 mg, 0.43 mmol), 1-bromo-2-methylbenzene (62 μL, 0.52 mmol), $Pd_2(dba)_3$ (24 mg, 0.02 mmol), BINAP (31 mg, 0.05 mmol), and NaOBu^t (171 mg, 1.8 mmol) were stirred in anhydrous toluene (8 mL) at 100 °C for 2 h. The reaction mixture was cooled to room temperature, and water was added to quench the reaction. The insoluble materials of the mixture were removed by filtration. The organic compound was extracted with Et_2O (30 mL), washed with H_2O (25 mL × 3) and brine (25 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel flash column chromatography to give (*S*)-**12b** (PE/EA = 50/1, 128.7 mg) and (*S*)-**11b** (PE/EA = 10/1, 87 mg), respectively. Compounds (*S*)-**12c−g** and (*S*)-**11c−g** were prepared in a similar method from the different aryl bromides.

(*S*)-**11b**: white solid, 36% yield. Anal. Calcd for $C_{39}H_{32}N_4$ (M = 556.26 g mol^{-1}): C, 84.14; H, 5.79; N, 10.06. Found: C, 83.98; H, 5.83; N, 9.98. ^{1}H NMR (400 MHz): δ 7.88−7.84 (m, 2H, Ar), 7.81−7.78 (m, 2H, Ar), 7.39 (d, J = 9.2 Hz, 1H, Ar), 7.31−6.94 (m, 15H, Ar), 6.89−6.86 (m, 2H, Ar), 6.70−6.63 (m, 2H, Ar), 5.48 (s, 2H, NH), 5.10 (s, 1H, NH), 3.65 (br s, 2H, NH_2), 1.91 (s, 3H, CH_3). ^{13}C

https://dx.doi.org/10.1021/acs.organomet.0c00036
Organometallics XXXX, XXX, XXX−XXX

NMR (100 MHz): δ 143.0, 142.6, 141.9, 138.6, 133.8, 133.7, 131.6, 130.7, 129.8, 129.7, 129.2, 128.7, 128.4, 128.3, 127.5, 127.1, 125.8, 125.6, 125.5, 125.1, 124.0, 123.5, 123.3, 122.8, 121.9, 121.1 (Ar), 17.6 (CH_3). HRMS (positive ions): m/z calcd for $C_{39}H_{33}N_4$ $[M + H]^+$, 557.2705; found, 557.2702.

(*S*)-**12b**: light yellow solid, 46% yield. Anal. Calcd for $C_{46}H_{38}N_4$ (M = 646.82 g mol^{-1}): C, 85.42; H, 5.92; N, 8.66. Found: C, 85.33; H, 6.03; N, 8.77. ^{1}H NMR (400 MHz): δ 7.83−7.81 (m, 4H, Ar), 7.34−7.26 (m, 3H, Ar), 7.21−7.11 (m, 7H, Ar), 7.07−6.95 (m, 8H, Ar), 6.91−6.84 (m, 4H, Ar), 6.82−6.78 (m, 2H, Ar), 5.48 (br s, 2H, NH), 5.39 (br s, 2H, NH), 1.88 (s, 3H, CH_3). ^{13}C NMR (100 MHz): δ 141.9, 140.9, 138.8, 133.8, 131.5, 130.9, 129.9, 129.2, 128.7, 128.5, 127.3, 126.8, 125.3, 124.2, 123.8, 123.3, 122.1, 121.1, 118.8, 117.5, 117.0, 115.0 (Ar), 17.7 (CH_3). HRMS (positive ions): m/z calcd for $C_{46}H_{39}N_4$ $[M + H]^+$, 647.3175; found, 647.3181.

(*S*)-**11c**: white solid, 55% yield. Anal. Calcd for $C_{39}H_{32}N_4O$ (M = 572.70 g mol^{-1}): C, 81.79; H, 5.63; N, 9.78. Found: C, 81.58; H, 5.75; N, 9.81. ^{1}H NMR (400 MHz): δ 7.86−7.83 (m, 2H, Ar), 7.77−7.73 (m, 2H, Ar), 7.40 (d, J = 8.8 Hz, 1H, Ar), 7.31−7.13 (m, 8H, Ar), 7.05−6.88 (m, 6H, Ar), 6.79−6.62 (m, 5H, Ar), 6.03 (br s, 1H, NH), 5.54 (br s, 1H, NH), 5.54 (br s, 1H, NH), 3.60 (br s, 2H, NH_2), 3.49 (s, 3H, OCH_3). ^{13}C NMR (100 MHz): δ 148.5, 143.5, 142.7, 141.8, 137.0, 133.9, 133.8, 133.3, 132.9, 129.7, 129.6, 129.3, 128.6, 128.4, 128.3, 127.4, 127.3, 127.1, 126.9, 126.6, 124.6, 124.1, 123.7, 123.4, 123.2, 122.6, 122.1, 120.8, 120.1, 119.2, 118.7, 117.3, 116.0, 115.7, 115.5, 115.0, 113.1, 110.5 (Ar), 55.4 (OCH_3). HRMS (positive ions): m/z calcd for $C_{39}H_{33}N_4O$ $[M + H]^+$, 573.2654; found, 573.2657.

(*S*)-**12c**: light yellow solid, 32% yield. Anal. Calcd for $C_{46}H_{38}N_4O_2$ (M = 678.82 g mol^{-1}): C, 81.39; H, 5.64; N, 8.25. Found: C, 81.28; H, 5.76; N, 8.34. ^{1}H NMR (400 MHz): δ 7. 78−7.74 (m, 4H, Ar), 7.30−7.22 (m, 4H, Ar), 7.19−7.10 (m, 6H, Ar), 7.01−6.95 (m, 4H, Ar), 6.83−6.67 (m, 8H, Ar), 6.08 (br s, 2H, NH), 5.47 (br s, 2H, NH), 3.48 (s, 6H, OCH_3). ^{13}C NMR (100 MHz): δ 148.5, 141.7, 137.3, 133.8, 132.9, 132.7, 129.6, 129.1, 128.2, 126.7, 124.6, 124.0, 123.9, 122.9, 121.8, 120.7, 120.0, 118.5, 117.0, 115.1, 115.0, 110.4 (Ar), 55.3 (OCH_3). HRMS (positive ions): m/z calcd for $C_{46}H_{39}N_4O_2$ $[M + H]^+$, 679.3073; found, 679.3081.

(*S*)-**11d**: white solid, 43% yield. Anal. Calcd for $C_{40}H_{34}N_4$ (M = 570.72 g mol^{-1}): C, 84.18; H, 6.00; N, 9.82. Found: C, 84.09; H, 6.04; N, 9.90. ^{1}H NMR (400 MHz): δ 7.89−7.84 (m, 2H, Ar), 7.79 (d, J = 8.4 Hz, 2H, Ar), 7.38 (d, J = 8.8 Hz, 1H, Ar), 7.33−7.23 (m, 3H, Ar), 7.21−6.92 (m, 11H, Ar), 6.83 (t, J = 7.2 Hz, 1H, Ar), 6.71−6.63 (m, 2H, Ar), 5.61 (s, 1H, NH), 5.54 (s, 1H, NH), 5.10 (s, 1H, NH), 3.62 (br s, 2H, NH_2), 3.28 (q, J = 7.6 Hz, 2H, CH_2), 0.97 (t, J = 7.6 Hz, 3H, CH_3). ^{13}C NMR (100 MHz): δ 143.1, 142.6, 142.1, 140.2, 139.5, 134.7, 133.8, 131.2, 129.8, 129.7, 129.2, 128.7, 128.4, 127.5, 127.1, 126.9, 126.6, 125.3, 124.3, 124.0, 123.6, 123.2, 122.8, 122.5, 120.7, 119.8, 118.8, 117.0, 116.9, 116.1, 115.8, 115.0, 113.2 (Ar), 24.1 (CH_2), 13.6 (CH_3). HRMS (positive ions): m/z calcd for $C_{40}H_{35}N_4$ $[M + H]^+$, 571.2862; found, 571.2863.

(*S*)-**12d**: light yellow solid, 37% yield. Anal. Calcd for $C_{48}H_{42}N_4$ (M = 674.87 g mol^{-1}): C, 85.43; H, 6.27; N, 8.30. Found: C, 85.31; H, 6.14; N, 8.44. ^{1}H NMR (400 MHz): δ 7.85−7.81 (m, 4H, Ar), 7.35−7.29 (m, 3H, Ar), 7.23−7.05 (m, 11H, Ar), 7.00−6.93 (m, 8H, Ar), 6.78 (t, J = 7.2 Hz, 2H, Ar), 5.61 (br s, 2H, NH), 5.39 (br s, 2H, NH), 2.28 (q, J = 7.6 Hz, 4H, CH_2), 0.98 (t, J = 7.6 Hz, 6H, CH_3). ^{13}C NMR (100 MHz): δ 142.0, 140.1, 139.6, 134.8, 133.7, 130.9, 129.7, 129.1, 128.7, 128.3, 127.1, 126.5, 125.4, 124.5, 123.8, 123.2, 122.5, 120.6, 119.9, 116.9, 114.7 (Ar), 24.1 (CH_2), 13.6 (CH_3). HRMS (positive ions): m/z calcd for $C_{48}H_{43}N_4$ $[M + H]^+$, 675.3488; found, 675.3487.

(*S*)-**11e**: white solid, 46% yield. Anal. Calcd for $C_{41}H_{36}N_4$ (M = 584.75 g mol^{-1}): C, 84.21; H, 6.21; N, 9.58. Found: C, 84.06; H, 6.31; N, 9.60. ^{1}H NMR (400 MHz): δ 7.90−7.81 (m, 4H, Ar), 7.37−7.25 (m, 6H, Ar), 7.27 (d, J = 6.4 Hz, 2H, Ar), 7.17 (t, J = 7.2 Hz, 2H, Ar), 7.11−6.98 (m, 6H, Ar), 6.91 (d, J = 8.0 Hz, 1H, Ar), 6.81 (t, J = 7.2 Hz, 1H, Ar), 6.72−6.65 (m, 2H, Ar), 5.74 (s, 1H, NH), 5.43 (s, 1H, NH), 5.15 (s, 1H, NH), 3.61 (br s, 2H, NH_2), 2.85 (m, 1H, CH), 1.03 (d, J = 6.8 Hz, 6H, CH_3). ^{13}C NMR (100 MHz): δ 143.1, 142.7, 142.4, 140.9, 140.6, 139.2, 133.8, 130.3, 129.8, 129.7, 129.1, 128.7, 128.4, 127.5, 127.1, 127.0, 126.6, 126.4, 125.9, 125.7, 125.0, 123.9, 123.6, 123.4, 123.2, 122.8, 121.8, 120.0, 118.8, 117.0, 116.1, 115.8, 115.7, 114.7, 113.2 (Ar), 27.7 (CH), 22.8, 22.7 (CH_3). HRMS (positive ions): m/z calcd for $C_{41}H_{37}N_4$ $[M + H]^+$, 585.3018; found, 585.3021.

(*S*)-**12e**: light yellow solid, 20% yield. Anal. Calcd for $C_{50}H_{46}N_4$ (M = 702.93 g mol^{-1}): C, 85.43; H, 6.60; N, 7.97. Found: C, 85.31; H, 6.57; N, 8.01. ^{1}H NMR (400 MHz): δ 7.87−7.82 (m, 4H, Ar), 7.32−7.21 (m, 10H, Ar), 7.10−6.98 (m, 10H, Ar), 6.89 (t, J = 8.8 Hz, 2H, Ar), 6.74 (t, J = 7.6 Hz, 2H, Ar), 5.72 (br s, 2H, NH), 5.37 (br s, 2H, NH), 2.87−2.81 (m, 2H, CH), 1.02 (d, J = 7.6 Hz, 12H, CH_3). ^{13}C NMR (100 MHz): δ 142.3, 141.1, 140.8, 139.1, 133.7, 129.9, 129.8, 129.0, 128.4, 127.1, 126.4, 125.9, 125.8, 125.3, 123.8, 123.5, 123.1, 122.0, 119.8, 116.8, 115.3, 114.4 (Ar), 27.7 (CH), 22.8, 22.7 (CH_3). HRMS (positive ions): m/z calcd for $C_{50}H_{47}N_4$ $[M + H]^+$, 703.3801; found, 703.3799.

(*S*)-**11f**: white solid, 16% yield. Anal. Calcd for $C_{44}H_{34}N_4$ (M = 618.77 g mol^{-1}): C, 85.41; H, 5.54; N, 9.05. Found: C, 85.29; H, 5.71; N, 8.96. ^{1}H NMR (400 MHz): δ 7.87 (d, J = 8.4 Hz, 2H, Ar), 7.75 (d, J = 8.8 Hz, 2H, Ar), 7.45 (d, J = 8.8 Hz, 1H, Ar), 7.39−7.32 (m, 2H, Ar), 7.22−7.08 (m, 10H, Ar), 7.05−6.86 (m, 10H, Ar), 6.68−6.61 (m, 2H, Ar), 5.56 (s, 1H, NH), 5.53 (s, 1H, NH), 4.89 (s, 1H, NH), 3.55 (br s, 2H, NH). ^{13}C NMR (100 MHz): δ 143.3, 142.5, 141.3, 140.5, 138.6, 136.5, 134.3, 133.8, 133.6, 131.3, 130.5, 129.6, 129.3, 129.0, 128.5, 128.3, 128.2, 128.0, 127.3, 127.0, 126.6, 124.1, 124.0, 123.4, 123.3, 122.8, 122.7, 121.9, 120.9, 120.2, 118.6, 117.4, 117.3, 115.9, 115.6, 112.9 (Ar). HRMS (positive ions): m/z calcd for $C_{44}H_{35}N_4$ $[M + H]^+$, 619.2862; found, 619.2864.

(*S*)-**11g**: white solid, 39% yield. Anal. Calcd for $C_{42}H_{32}N_4$ (M = 592.73 g mol^{-1}): C, 85.11; H, 5.44; N, 9.45. Found: C, 85.02; H, 5.67; N, 9.54. ^{1}H NMR (400 MHz): δ 7.91−7.80 (m, 3H, Ar), 7.77−7.74 (m, 2H, Ar), 7.65 (d, J = 8.4 Hz, 1H, Ar), 7.70−7.42 (m, 3H, Ar), 7.32−7.24 (m, 6H, Ar), 7.19−7.15 (m, 2H, Ar), 7.191−6.87 (m, 8H, Ar), 6.65 (dd, J = 8.8 Hz, 1.2 Hz, 1H, Ar), 6.59 (t, J = 7.6 Hz, 1H, Ar), 6.22 (br s, 1H, NH), 5.54 (br s, 1H, NH), 5.10 (s, 1H, NH), 3.58 (br s, 2H, NH). ^{13}C NMR (100 MHz): δ 143.0, 142.6, 142.0, 139.5, 138.3, 134.5, 133.8, 133.6, 131.2, 129.8, 129.2, 128.6, 128.4, 128.3, 127.5, 127.2, 127.1, 126.9, 126.5, 125.9, 125.6, 125.4, 124.7, 123.9, 123.4, 123.3, 122.8, 122.6, 121.5, 121.2, 118.8, 117.7, 116.9, 116.1, 115.8, 115.1, 114.8, 113.2 (Ar). HRMS (positive ions): m/z calcd for $C_{42}H_{33}N_4$ $[M + H]^+$, 593.2705; found, 593.2707.

(*S*)-**12g**: white solid, 41% yield. Anal. Calcd for $C_{52}H_{38}N_4$ (M = 718.88 g mol^{-1}): C, 86.88; H, 5.33; N, 7.79. Found: C, 86.69; H, 5.55; N, 7.83. ^{1}H NMR (400 MHz): δ 7.81−7.75 (m, 6H, Ar), 7.61 (d, J = 7.6 Hz, 2H, Ar), 7.46−7.36 (m, 6H, Ar), 7.28−6.98 (m, 18H, Ar), 6.78 (t, J = 7.6 Hz, 2H, Ar), 6.13 (br s, 2H, NH), 5.49 (br s, 2H, NH). ^{13}C NMR (100 MHz): δ 141.8, 139.3, 138.4, 134.6, 133.6, 131.2, 129.8, 129.1, 128.4, 128.3, 127.2, 125.9, 125.5, 125.3, 124.6, 123.6, 123.2, 122.5, 121.5, 121.2, 117.8, 116.7, 115.0, 114.8 (Ar). HRMS (positive ions): m/z calcd for $C_{52}H_{39}N_4$ $[M + H]^+$, 719.3175; found, 719.3181.

Synthesis of Intermediates (*S*)-13b−g. Under an argon atmosphere, a mixture of (*S*)-**11b** (200 mg, 0.36 mmol), bromobenzene (45 μL, 0.43 mmol), $Pd_2(dba)_3$ (20 mg, 0.02 mmol), BINAP (26 mg, 0.042 mmol), and $NaOBu^t$ (171 mg, 1.5 mmol) were stirred in anhydrous toluene (7 mL) at 100 °C for 2 h. The reaction mixture was cooled to room temperature, and water was added to quench the reaction. The insoluble materials of the mixture were removed by filtration. The organic compound was extracted with Et_2O (30 mL), washed with H_2O (25 mL × 3) and brine (25 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by silica gel flash column chromatography to give (*S*)-**13b** (196 mg). Compounds (*S*)-**13c−g** were prepared in a similar method from (*S*)-**11c−g**.

(*S*)-**13b**: light yellow solid, 68% yield. Anal. Calcd for $C_{45}H_{36}N_4$ (M = 632.79 g mol^{-1}): C, 85.41; H, 5.73; N, 8.85. Found: C, 85.37; H, 5.81; N, 8.92. ^{1}H NMR (400 MHz): δ 7.84 (t, J = 7.2 Hz, 4H, Ar), 7.39−7.13 (m, 13H, Ar), 7.10−7.02 (m, 5H, Ar), 6.94−6.85 (m, 5H, Ar), 6.75 (d, J = 7.6 Hz, 2H, Ar), 5.47 (br s, 4H, NH), 1.91 (s, 3H,

https://dx.doi.org/10.1021/acs.organomet.0c00036
Organometallics XXXX, XXX, XXX−XXX

CH_3). ^{13}C NMR (100 MHz): δ 142.6, 141.7, 140.7, 138.5, 138.0, 133.6, 131.4, 130.6, 129.7, 129.0, 128.3, 128.2, 127.1, 126.5, 125.0, 124.3, 123.8, 123.7, 123.6, 123.1, 122.8, 121.3, 121.1, 120.9, 118.5, 117.9, 117.4, 117.3, 116.8, 116.6, 114.8, 114.7 (Ar), 17.5 (CH_3). HRMS (positive ions): m/z calcd for $C_{45}H_{37}N_4$ $[M + H]^+$, 633.3018; found, 633.3028.

(*S*)-**13c**: light yellow solid, 62% yield. Anal. Calcd for $C_{45}H_{36}N_4O$ (M = 648.79 g mol^{-1}): C, 83.31; H, 5.59; N, 8.64. Found: C, 83.22; H, 5.64; N, 8.71. ^1H NMR (400 MHz): δ 7. 81−7.13 (m, 4H, Ar), 7.37 (d, J = 8.8 Hz, 1H, Ar), 7.29−7.09 (m, 11H, Ar), 7.03−6.98 (m, 3H, Ar), 6.92−6.66 (m, 10H, Ar), 6.03 (s, 1H, NH), 5.72 (s, 1H, NH), 5.48 (s, 1H, NH), 5.33 (s, 1H, NH), 3.48 (s, 3H, OCH_3). ^{13}C NMR (100 MHz): δ 148.4, 142.6, 141.8, 141.6, 138.6, 136.8, 133.86, 133.7, 133.2, 132.7, 131.2, 129.7, 129.6, 129.2, 129.1, 128.9, 128.4, 128.2, 127.1, 126.9, 125.2, 125.1, 124.5, 123.8, 123.3, 123.2, 122.9, 122.1, 121.1, 120.9, 120.7, 120.0, 119.1, 118.0, 117.2, 116.9, 116.4, 115.3, 114.9, 114.5, 110.4 (Ar), 55.3 (OCH_3). HRMS (positive ions): m/z calcd for $C_{45}H_{37}N_4O$ $[M + H]^+$, 649.2967; found, 649.2970.

(*S*)-**13d**: light yellow solid, 79% yield. Anal. Calcd for $C_{46}H_{38}N_4$ (M = 646.82 g mol^{-1}): C, 85.42; H, 5.92; N, 8.66. Found: C, 85.37; H, 6.00; N, 8.74. ^1H NMR (400 MHz): δ 7. 82−7.78 (m, 4H, Ar), 7.32−7.20 (m, 3H, Ar), 7.18−7.08 (m, 9H, Ar), 7.03−6.90 (m, 7H, Ar), 6.85−6.77 (m, 4H, Ar), 6.71 (d, J = 7.6 Hz, 2H, Ar), 5.64 (br s, 1H, NH), 5.57 (br s, 1H, NH), 5.36 (s, 1H, NH), 5.34 (s, 4H, NH), 2.24 (q, J = 7.6 Hz, 2H, CH_2), 0.93 (t, J = 7.6 Hz, 3H, CH_3). ^{13}C NMR (100 MHz): δ 142.6, 142.0, 141.7, 140.1, 139.5, 138.1, 134.7, 133.7, 131.6, 131.1, 129.8, 129.7, 129.1, 128.7, 128.4, 128.3, 127.2, 127.1, 126.5, 125.3, 125.1, 124.4, 124.3, 123.8, 123.2, 123.1, 122.5, 121.4, 121.0, 120.7, 119.8, 118.0, 117.4, 116.9, 116.8, 116.7, 114.9, 114.8 (Ar), 24.1 (CH_2), 13.6 (CH_3). HRMS (positive ions): m/z calcd for $C_{46}H_{39}N_4$ $[M + H]^+$, 647.3175; found, 6647.3178.

(*S*)-**13e**: light yellow solid, 93% yield. Anal. Calcd for $C_{47}H_{40}N_4$ (M = 660.85 g mol^{-1}): C, 85.42; H, 6.10; N, 8.48. Found: C, 85.39; H, 6.14; N, 8.51. ^1H NMR (400 MHz): δ 7.85−7.81 (m, 4H, Ar), 7.40−7.02 (m, 20H, Ar), 6.92−6.83 (m, 3H, Ar), 6.78−6.74 (m, 3H, Ar), 5.70 (s, 2H, NH), 5.39 (s, 1H, NH), 5.35 (s, 1H, NH), 2.86−2.79 (m, 1H, CH), 1.01 (d, J = 6.8 Hz, 6H, CH_3). ^{13}C NMR (100 MHz): δ 142.6, 142.3, 141.8, 140.9, 140.6, 139.1, 138.2, 133.8, 133.7, 131.5, 130.1, 129.8, 129.1, 128.4, 127.2, 127.1, 126.4, 125.9, 125.7, 125.2, 125.0, 124.6, 123.8, 123.7, 123.4, 123.2, 121.8, 121.4, 121.0, 118.0, 117.3, 116.9, 116.7, 115.5, 114.8, 114.6 (Ar), 27.7 (CH), 22.8, 22.7 (CH_3). HRMS (positive ions): m/z calcd for $C_{47}H_{41}N_4$ $[M + H]^+$, 661.3331; found, 6661.3333.

(*S*)-**13f**: white solid, 73% yield. Anal. Calcd for $C_{50}H_{38}N_4$ (M = 694.86 g mol^{-1}): C, 86.42; H, 5.51; N, 8.06. Found: C, 86.29; H, 5.62; N, 8.23. ^1H NMR (400 MHz): δ 7.87−7.83 (m, 2H, Ar), 7.78−7.76 (m, 2H, Ar), 7.41 (d, J = 8.8 Hz, 2H, Ar), 7.36−7.32 (m, 2H, Ar), 7.29−7.20 (m, 6H, Ar), 7.18−6.83 (m, 21H, Ar), 6.81 (t, J = 8.0 Hz, 1H, Ar), 6.74 (d, J = 8.0 Hz, 2H, Ar), 5.67 (s, 1H, NH), 5.55 (s, 1H, NH), 5.50 (s, 1H, NH), 5.14 (s, 1H, NH). ^{13}C NMR (100 MHz): δ 142.6, 141.8, 141.3, 140.4, 138.7, 138.6, 136.5, 134.1, 133.8, 133.6, 131.2, 131.1, 130.6, 129.7, 129.3, 129.1, 129.0, 128.9, 128.5, 128.4, 128.3, 124.0, 123.9, 123.7, 123.3, 123.1, 122.9, 122.1, 121.1, 121.0, 120.9, 120.1, 118.3, 117.3, 117.2, 116.8, 116.5, 115.8, 114.5 (Ar). HRMS (positive ions): m/z calcd for $C_{50}H_{39}N_4$ $[M + H]^+$, 695.3175; found, 695.3179.

(*S*)-**13g**: white solid, 78% yield. Anal. Calcd for $C_{48}H_{36}N_4$ (M = 668.83 g mol^{-1}): C, 86.20; H, 5.43; N, 8.38. Found: C, 86.11; H, 5.50; N, 8.51. ^1H NMR (400 MHz): δ 7.87−7.72 (m, 2H, Ar), 7.0 (d, J = 8.8 Hz, 1H, Ar), 7.48−7.38 (m, 3H, Ar), 7.30−7.21 (m, 3H, Ar), 7.19−7.12 (m, 5H, Ar), 7.10−7.04 (m, 4H, Ar), 7.02−7.00 (m, 3H, Ar), 6.95 (t, J = 7.6 Hz, 1H, Ar), 6.87−6.80 (m, 2H, Ar), 6.75 (t, J = 7.6 Hz, 1H, Ar), 6.67 (d, J = 8.0 Hz, 2H, Ar), 6.15 (s, 1H, NH), 5.59 (s, 1H, NH), 5.47 (s, 1H, NH), 5.33 (s, 1H, NH). ^{13}C NMR (100 MHz): δ 142.8, 141.9, 141.7, 139.4, 138.3, 137.9, 134.6, 133.7, 133.6, 131.7, 131.2, 129.9, 129.8, 129.1, 129.0, 128.5, 128.4, 128.3, 127.3, 127.2, 125.9, 125.6, 125.4, 125.0, 124.7, 124.3, 123.7, 123.6, 123.2, 122.6, 121.5, 121.2, 120.9, 117.8, 117.7, 116.8, 116.6, 115.0, 114.9 (Ar). HRMS (positive ions): m/z calcd for $C_{48}H_{37}N_4$ $[M + H]^+$, 669.3018; found, 669.3015.

Synthesis of Palladium Complexes (*S*)-7b−g. In a round-bottomed flamed flask (25 mL) equipped with a rubber septum and magnetic stirbar were placed (*S*)-**9** (190 mg, 0.55 mmol) and $HC(OEt)_3$ (6.0 mL). Then, 12.1 N HCl (60 μL) was added dropwise using a syringe. The resulting suspension was stirred at room temperature for 30 min under argon and then heated to 80 °C and continuously stirred for 3 h. After the mixture was cooled to room temperature, the volatile material was removed under vacuum and the residue was washed several times with diethyl ether/hexane, followed by removal of residual solvents under high vacuum to afford H_2[(*S*)-**3b**]Cl_2 as a yellow solid. Under an argon atmosphere, a mixture of H_2[(*S*)-**3b**]Cl_2 (216 mg, 0.30 mmol) and $Pd_2(dba)_3$ (333 mg, 0.36 mmol) was stirred in anhydrous THF (18 mL) under reflux for 4 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel to give (*S*)-**7b**. Complexes (*S*)-**7c−g** were prepared in a similar method from (*S*)-**13c−g**.

(*S*)-**7b** (+**7b′**): white solid, 54% yield. ^1H NMR (400 MHz): δ 8.21 (d, J = 6.8 Hz, 1H, Ar), 8.16−8.06 (m, 6H, Ar), 8.01 (d, J = 8.4 Hz, 1H, Ar), 7.96 (d, J = 8.4 Hz, 1H, Ar), 7.09−7.87 (m, 4H, Ar), 7.76 (d, J = 8.0 Hz, 1H, Ar), 7.67 (d, J = 8.4 Hz, 2H, Ar), 7.50 (d, J = 8.8 Hz, 1H, Ar), 7.41−7.22 (m, 20H, Ar), 7.16−6.90 (m, 18H, Ar), 6.68 (d, J = 7.6 Hz, 1H, Ar), 6.64−6.62 (m, 1H, Ar), 2.33 (s, 3H, CH_3), 1.55 (s, 3H, CH_3). ^{13}C NMR (100 MHz): δ 198.4 (minor), 197.7 (major) (C−Pd), 180.7 (major), 180.3 (minor) (C−Pd), 150.2, 150.0, 147.7, 147.5, 137.4, 137.1, 137.0, 136.7, 136.1, 136.0, 135.9, 135.7, 134.8, 134.3, 133.7, 133.4, 132.9, 132.7, 132.5, 132.3, 132.0, 131.7, 131.2, 130.8, 130.3, 130.1, 130.0, 129.9, 129.7, 129.0, 128.9, 128.7, 128.6, 128.0, 127.7, 127.6, 127.4, 127.3, 127.1, 127.0, 126.9, 126.7, 126.4, 126.3, 126.1, 125.9, 125.7, 125.0, 124.3, 124.2, 123.3, 123.2, 122.9, 122.8, 122.5, 122.3, 112.3, 112.1, 111.6, 111.5, 111.4, 111.0, 110.9 (Ar), 19.3, 18.7 (CH_3). Anal. Calcd for $C_{47}H_{31}ClN_4Pd$ (M = 793.6488 g mol^{-1}): C, 71.13; H, 3.94; N, 7.06. Found: C, 71.05; H, 3.40; N, 7.11.

(*S*)-**7c** (+**7c′**): white solid, 59% yield. ^1H NMR (400 MHz): δ (major) 8.26−8.24 (m, 1H, Ar), 8.16−7.61 (m, 8H, Ar), 7.39−6.87 (m, 17H, Ar), 6.76−6.74 (m, 1H, Ar), 6.61 (d, J = 7.6 Hz, 1H, Ar), 3.82 (s, 3H, OCH_3); (minor), 8.55 (d, J = 7.6 Hz, 1H, Ar), 8.16−7.61 (m, 8H, Ar), 7.39−6.87 (m, 18H, Ar), 6.76−6.74 (m, 1H, Ar), 3.57 (s, 3H, OCH_3). ^{13}C NMR (100 MHz): δ 198.1 (minor), 197.2 (major) (C−Pd), 180.9 (major), 179.9 (minor) (C−Pd), 154.8 (major), 154.2 (minor), 150.4, 150.2, 147.8, 147.6, 137.3, 137.0, 135.9, 134.8, 133.6, 133.3, 132.7, 132.6, 132.3, 132.1, 131.9, 131.7, 131.0, 130.1, 130.0, 129.9, 128.7, 128.6, 128.3, 127.6, 127.4, 127.3, 127.1, 126.9, 126.7, 126.2, 126.0, 125.9, 125.7, 125.3, 124.7, 124.6, 124.1, 123.2, 122.4, 122.0, 121.0, 120.5, 112.9, 112.2, 112.1, 112.0, 111.9, 111.5, 111.4, 111.3, 111.1 (Ar), 56.2 (major), 55.2 (minor) (OCH_3). Anal. Calcd for $C_{47}H_{31}ClN_4OPd$ (M = 809.6482 g mol^{-1}): C, 69.72; H, 3.86; N, 6.92. Found: C, 69.66; H, 3.94; N, 7.07.

(*S*)-**7d** (+**7d′**): white solid, 52% yield. ^1H NMR (400 MHz): δ 8.18−8.14 (m, 4H, Ar), 8.08−8.06 (m, 1H, Ar), 8.01−7.95 (m, 3H, Ar), 7.89−7.87 (m, 3H, Ar), 7.76 (d, J = 8.0 Hz, 1H, Ar), 7.65 (d, J = 8.0 Hz, 1H, Ar), 7.52 (d, J = 7.6 Hz, 1H, Ar), 7.45−6.85 (m, 20H, Ar), 6.66−6.60 (m, 2H, Ar), 2.89, 2.36 (m, 2H, CH_2), 1.26 (t, J = 7.6 Hz, 3H, CH_3). ^{13}C NMR (100 MHz): δ 198.3 (minor), 197.7 (mjor) (C−Pd), 180.6 (minor), 180.2 (major) (C−Pd), 150.2 (minor), 149.9 (major), 147.7 (minor), 147.4 (minor), 137.3, 137.1, 137.0, 136.4, 136.1, 136.0, 135.9, 135.3, 134.6, 134.2, 134.1, 133.6, 133.5, 133.4, 132.8, 132.7, 132.3, 131.9, 131.6, 131.1, 130.0, 129.8, 129.5, 129.2, 129.1, 128.7, 128.6, 127.9, 127.6, 127.4, 127.3, 127.0, 126.9, 126.4, 126.2, 126.0, 125.8, 125.7, 124.9, 124.7, 124.2, 124.1, 123.3, 122.9, 122.6, 122.4, 122.3, 112.3, 112.2, 112.1, 111.5, 111.4, 110.9 (Ar), 23.7 (minor), 23.5 (major) (CH_2), 13.9 (major), 13.0 (minor) (CH_3). Anal. Calcd for $C_{48}H_{33}ClN_4Pd$ (M = 807.6754 g mol^{-1}): C, 71.38; H, 4.12; N, 6.94. Found: C, 71.27; H, 4.27; N, 7.06.

(*S*)-**7e** (+**7e′**): white solid, 46% yield. ^1H NMR (400 MHz): δ (major) 8.17−8.10 (m, 2H, Ar), 8.07−8.00 (m, 2H, Ar), 7.86 (d, J = 8.4 Hz, 2H, Ar), 7.57 (d, J = 8.8 Hz, 1H, Ar), 7.40−7.19 (m, 11H, Ar), 7.11−7.05 (m, 3H, Ar), 7.03−6.90 (m, 4H, Ar), 6.63 (d, J = 7.6 Hz, 1H, Ar), 2.19 (m, 1H, CH), 1.21 (d, J = 6.8 Hz, 3H, CH_3), 0.61

https://dx.doi.org/10.1021/acs.organomet.0c00036
Organometallics XXXX, XXX, XXX−XXX

(d, J = 6.8 Hz, 3H, CH_3); (minor) 8.19−6.63 (m, 28H, Ar), 2.94 (m, 1H, CH), 1.40 (d, J = 6.8 Hz, 3H, CH_3), 1.18 (d, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz): δ 197.7 (major) (C−Pd), 180.4 (minor), 180.2 (major) (C−Pd), 150.1, 147.5, 145.2, 137.3, 137.0, 136.9, 135.9, 134.3, 134.2, 133.4, 132.8, 132.7, 132.3, 131.8, 131.6, 131.2, 129.8, 129.4, 129.3, 128.7, 128.4, 127.7, 127.6, 127.3, 127.1, 126.9, 126.3, 126.2, 126.0, 125.6, 125.5, 124.8, 124.7, 124.2, 123.3, 122.9, 122.4, 112.3, 112.2, 112.1, 111.5, 110.9 (Ar), 28.1 (CH, minor), 27.1 (CH, major), 25.7 (CH_3, minor), 24.7 (CH_3, major), 24.4 (CH_3, minor), 23.9 (CH_3, major). Anal. Calcd for $C_{49}H_{35}ClN_4Pd$ (M = 821.7020 g mol^{-1}): C, 71.62; H, 4.29; N, 6.82. Found: C, 71.51; H, 4.38; N, 6.99.

(*S*)-**7f**: white solid, 37% yield. ^{1}H NMR (400 MHz): δ 8.24−8.19 (m, 1H, Ar), 8.14−8.12 (m, 1H, Ar), 7.90−7.83 (m, 4H, Ar), 7.64−7.59 (m, 3H, Ar), 7.56−7.53 (m, 2H, Ar), 7.43−7.29 (m, 5H, Ar), 7.22−6.95 (m, 12H, Ar), 6.77 (d, J = 8.0 Hz, 1H, Ar), 6.56 (t, J = 7.6 Hz, 1H, Ar), 6.38 (d, J = 7.6 Hz, 1H, Ar), 6.19 (d, J = 8.4 Hz, 1H, Ar). ^{13}C NMR (100 MHz): δ 197.5 (C−Pd), 180.5 (C−Pd), 150.2, 147.8, 143.3, 138.9, 137.3, 137.2, 137.1, 136.2, 135.7, 134.6, 133.4, 132.5, 132.2, 131.8, 131.1, 130.1, 130.0, 129.3, 129.0, 128.7, 128.4, 128.3, 128.1, 128.0, 127.5, 127.2, 127.1, 127.0, 126.9, 126.8, 126.3, 125.9, 124.7, 124.6, 124.2, 123.2, 121.8, 121.7, 112.1, 111.9, 111.8, 111.4 (Ar). Anal. Calcd for $C_{52}H_{33}ClN_4Pd$ (M = 855.7182 g mol^{-1}): C, 72.99; H, 3.89; N, 6.55; Found: C, 72.79; H, 3.97; N, 6.71.

(*S*)-**7g** (+**7g′**): white solid, 47% yield. ^{1}H NMR (400 MHz): δ (major) 8.67 (d, J = 7.2 Hz, 1H, Ar), 8.20−8.10 (m, 4H, Ar), 7.90−7.62 (m, 7H, Ar), 7.46−6.82 (m, 17H, Ar), 6.44 (d, J = 8.0 Hz, 1H, Ar), 5.95 (d, J = 8.0 Hz, 1H, Ar). ^{13}C NMR (100 MHz): δ 198.9 (minor, C−Pd), 198.6 (major, C−Pd), 180.9 (minor, C−Pd), 180.0 (major, C−Pd), 149.9, 147.4, 137.4, 137.0, 136.4, 135.8, 134.4, 134.0, 133.9, 133.4, 133.0, 132.9, 132.7, 132.3, 132.0, 131.2, 129.8, 129.6, 129.4, 129.1, 128.4, 127.8, 127.7, 127.4, 127.1, 127.0, 126.2, 126.1, 125.8, 125.7, 125.2, 124.7, 124.3, 123.3, 123.0, 122.6, 112.2, 111.7, 111.3 (Ar). Anal. Calcd for $C_{50}H_{31}ClN_4Pd$ (M = 829.6809 g mol^{-1}): C, 72.38; H, 3.77; N, 6.75. Found: C, 72.27; H, 3.84; N, 6.90.

General Procedure for Asymmetric Aryl−Aryl Cross-Coupling Reactions. Aryl halides **14a−e** (0.2 mmol), arylboronic acids **15a−f** (0.3 mmol, 1.5 equiv), base (0.50 mmol, 2.5 equiv), and palladium catalysts (*S*)-**4a−d**, (*S*)-**5**, and (*S*)-**7a−g** (0.004 mmol, 0.02 equiv) together with solvent (5 mL) were introduced into an oven-dried Schlenk tube (25 mL). The mixture was deoxygenated three times using liquid dinitrogen, the flask was then sealed, and the mixture was stirred and heated to the desired temperature. After the reaction mixture was kept at a given temperature for 24 h, GC-MS was carried out, and then the mixture was treated with distilled water (10 mL), extracted with EA (3 × 10 mL), dried (Na_2SO_4), and purified by flash chromatography to give the biaryl products **16**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.0c00036.

Full ^{1}H and ^{13}C NMR spectra for bis-NHC-Pd complexes together with all relevant intermediates and typical GC and chiral HPLC characterization and analysis data (PDF)

Accession Codes

CCDC 1978451−1978452 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Dao Zhang − *Department of Chemistry, Fudan University, 200438 Shanghai, People's Republic of China*; orcid.org/0000-0002-5853-748X; Email: daozhang@fudan.edu.cn

Author

Jueqin Yu − *Department of Chemistry, Fudan University, 200438 Shanghai, People's Republic of China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.organomet.0c00036

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) (a) Loxq, P.; Manoury, E.; Poli, R.; Deydier, E.; Labande, A. Synthesis of axially chiral biaryl compounds by asymmetric catalytic reactions with transition metals. *Coord. Chem. Rev.* **2016**, *308*, 131−190. (b) Zhang, D.; Wang, Q. Palladium catalyzed asymmetric Suzuki−Miyaura coupling reactions to axially chiral biaryl compounds: Chiral ligands and recent advances. *Coord. Chem. Rev.* **2015**, *286*, 1−16. (c) Wencel-Delord, J.; Panossian, A.; Leroux, F. R.; Colobert, F. *Chem. Soc. Rev.* **2015**, *44*, 3418−3430. (d) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193−3207. (e) Baudoin, O. *Eur. J. Org. Chem.* **2005**, *2005*, 4223−4229. (f) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384−5427.

(2) (a) Cammidge, A. N.; Crepy, K. V. L. The First Asymmetric Suzuki Cross-Coupling Reaction. *Chem. Commun.* **2000**, 1723−1724. (b) Yin, J. J.; Buchwald, S. L. A Catalytic Asymmetric Suzuki Coupling for the Synthesis of Axially Chiral Biaryl Compounds. *J. Am. Chem. Soc.* **2000**, *122*, 12051−12052.

(3) For P-containing ligands, see: (a) Cammidge, A. N.; Crepy, K. V. L. Synthesis of Chiral Binaphthalenes using the Asymmetric Suzuki Reaction. *Tetrahedron* **2004**, *60*, 4377−4386. (b) Shen, X.; Jones, G. O.; Watson, D. A.; Bhayana, B.; Buchwald, S. L. Enantioselective Synthesis of Axially Chiral Biaryls by the Pd-Catalyzed Suzuki-Miyaura Reaction: Substrate Scope and Quantum Mechanical Investigations. *J. Am. Chem. Soc.* **2010**, *132*, 11278−11287. (c) Tang, W.; Patel, N. D.; Xu, G.; Xu, X.; Savoie, J.; Ma, S.; Hao, M.-H.; Keshipeddy, S.; Capacci, A. G.; Wei, X.; Zhang, Y.; Gao, J.; Li, W.; Rodriguez, S.; Lu, B. Z.; Yee, N. K.; Senanayake, C. H. Efficient Chiral Monophosphorous Ligands for Asymmetric Suzuki-Miyaura Coupling Reactions. *Org. Lett.* **2012**, *14*, 2258−2261. (d) Xu, G.; Fu, W.; Liu, G.; Senanayake, C. H.; Tang, W. Efficient Syntheses of Korupensamines A, B and Michellamine B by Asymmetric Suzuki-Miyaura Coupling Reactions. *J. Am. Chem. Soc.* **2014**, *136*, 570−574. (e) Patel, N. D.; Sieber, J. D.; Tcyrulnikov, S.; Simmons, B. J.; Rivalti, D.; Duvvuri, K.; Zhang, Y.; Gao, D. A.; Fandrick, K. R.; Haddad, N.; Lao, K. S.; Mangunuru, H. P. R.; Biswas, S.; Qu, B.; Grinberg, N.; Pennino, S.; Lee, H.; Song, J. J.; Gupton, B. F.; Garg, N. K.; Kozlowski, M. C.; Senanayake, C. H. Computationally Assisted Mechanistic Investigation and Development of Pd-Catalyzed Asymmetric Suzuki-Miyaura and Negishi Cross-Coupling Reactions for Tetra-ortho-Substituted Biaryl Synthesis. *ACS Catal.* **2018**, *8*, 10190−10209. (f) Genov, M.; Almorin, A.; Espinet, P. Efficient Synthesis of Chiral 1,1'-Binaphthalenes by the Asymmetric Suzuki-Miyaura Reactions: Dramatic Synthetic Improvement by Simple Purification of Naphthylboronic Acids. *Chem. - Eur. J.* **2006**, *12*, 9346−9352. (g) Wang, S.; Li, J.; Miao, T.; Wu, W.; Li, Q.; Zhuang, Y.; Zhou, Z.; Qiu, L.-Q. Highly Efficient Synthesis of a Class of Novel Chiral-Bridged Atropisomeric Monophosphine Ligands via Simple Desymmetrization and Their Applications in Asymmetric Suzuki-Miyaura Coupling Reaction. *Org. Lett.* **2012**, *14*, 1966−1969. (h) Zhou, Y.; Zhang, X.; Liang, H.; Cao, Z.; Zhao, X.; He, Y.;

https://dx.doi.org/10.1021/acs.organomet.0c00036
Organometallics XXXX, XXX, XXX−XXX

Wang, S.; Pang, J.; Zhou, Z.; Ke, Z.; Qiu, L.-Q. Enantioselective Synthesis of Axially Chiral Biaryl Monophosphine Oxides via Direct Asymmetric Suzuki Coupling and DFT Investigations of the Enantioselectivity. *ACS Catal.* **2014**, *4*, 1390−1397. (i) Xia, W.; Li, Y.; Zhou, Z.; Chen, H.; Liang, H.; Yu, S.; He, X.; Zhang, Y.; Pang, J.; Zhou, Z.; Qiu, L.-Q. Synthesis of Chiral-Bridged Atropisomeric Monophosphine Ligands with Tunable Dihedral Angles and their Applications in Asymmetric Suzuki-Miyaura Coupling Reactions. *Adv. Synth. Catal.* **2017**, *359*, 1656−1662. (j) Uozumi, Y.; Matsuura, T.; Arakawa, T.; Yamada, Y. M. A. Asymmetric Suzuki-Miyaura Coupling in Water with a Chiral Palladium Catalyst Supported on an Amphiphilic Resin. *Angew. Chem., Int. Ed.* **2009**, *48*, 2708−2710. (k) Uozumi, Y.; Matsuura, Y.; Suzuka, T.; Arakawa, T.; Yamada, Y. M. A. Palladium-Catalyzed Asymmetric Suzuki-Miyaura Cross Coupling with Homochiral Phosphine Ligands Having Tetrahydro-1H-imidazo-[1,5-a]indole Backbone. *Synthesis* **2016**, *49*, 59−68. (l) Yamamoto, T.; Akai, Y.; Nagata, Y.; Suginome, M. Highly Enantioselective synthesis of Axially Chiral biarylphosphonates: Asymmetric Suzuki-Miyaura Coupling Using High-Molecular-Weight, Helically Chiral Polyquinoxaline-Based Phosphines. *Angew. Chem., Int. Ed.* **2011**, *50*, 8844−8847. (m) Sawai, K.; Tatumi, R.; Nakahodo, T.; Fujihara, H. Asymmetric Suzuki-Miyaura Coupling Reactions Catalyzed by Chiral Palladium Nanoparticles at Room Temperature. *Angew. Chem., Int. Ed.* **2008**, *47*, 6917−6919.

(4) (a) Bermejo, A.; Ros, A.; Fernandez, R.; Lassaletta, J. M. C_2-Symmetric Bis-Hydrazones as Ligands in the Asymmetric Suzuki-Miyaura Cross-Coupling. *J. Am. Chem. Soc.* **2008**, *130*, 15798−15799. (b) Ros, A.; Estepa, B.; Bermejo, A.; Alvarez, E.; Fernandez, R.; Lassaletta, J. M. Phosphino Hydrazones as Suitable Ligands in the Asymmetric Suzuki-Miyaura Cross-Coupling. *J. Org. Chem.* **2012**, *77*, 4740−4750.

(5) Zhang, S.-S.; Wang, Z. Q.; Xu, M.-H.; Lin, G.-Q. Chiral Diene as the Ligand for the Synthesis of Axially chiral Compounds via the Palladium-Catalyzed Suzuki-Miyaura Coupling Reaction. *Org. Lett.* **2010**, *12*, 5546−5549.

(6) (a) Debono, N.; Labande, A.; Manoury, E.; Daran, J.-C.; Poli, R. Palladium Complexes of Planar Chiral Ferrocenyl Phosphine-NHC Ligands: New Catalysts for the Asymmetric Suzuki?Miyaura Reaction. *Organometallics* **2010**, *29*, 1879−1882. (b) Loxq, P.; Debono, N.; Gülcemal, S.; Daran, J.-C.; Manoury, E.; Poli, R.; Cetinkaya, B.; Labande, A. Palladium(II) complexes with planar chiral ferrocenyl phosphane−(benz)imidazol-2-ylidene ligands. *New J. Chem.* **2014**, *38*, 338−347. (c) Benhamou, L.; Besnard, C.; Kundig, E. P. Chiral PEPPSI Complexes: Synthesis, Characterization, and Application in Asymmetric Suzuki-Miyaura Coupling Reactions. *Organometallics* **2014**, *33*, 260−266. (d) Wu, L.- L.; Salvador, A.; Ou, A.; Shi, M.-W.; Skelton, B. W.; Dorta, R. Monodentate Chiral N-Heterocyclic Carbene-Palladium -Catalyzed Asymmetric Suzuki-Miyaura and Kumada Coupling. *Synlett* **2013**, *24*, 1215−1221. (e) Shen, D.; Xu, Y.; Shi, S.-L. A Bulky Chiral N-Heterocyclic Carbene Palladium Catalyst Enables Highly Enantioselective Suzuki-Miyaura Cross-Coupling Reactions for the Synthesis of Biaryl Atropisomers. *J. Am. Chem. Soc.* **2019**, *141*, 14938−14945.

(7) (a) Shigeng, G.; Tang, J.; Zhang, D.; Wang, Q.; Chen, Z.; Weng, L. Synthesis, structure, and catalytic activity of palladium complexes with new chiral cyclohexane-1,2-based di-NHC-ligands. *J. Organomet. Chem.* **2012**, *700*, 223−229. (b) Li, Y.; Tang, J.; Gu, J.; Wang, Q.; Sun, P.; Zhang, D. Chiral 1,2-CyclohexaneBridged Bis-NHC Palladium Catalysts for Asymmetric Suzuki-Miyaura Coupling: Synthesis, Characterization, and Steric Effects on Enantiocontrol. *Organometallics* **2014**, *33*, 876−884. (c) Zhang, D.; He, Y.; Tang, J. Chiral linker-bridged bis-N-heterocyclic carbenes: design, synthesis, palladium complexes, and catalytic properties. *Dalton Trans.* **2016**, *45*, 11699−11709. (d) Tang, J.; He, Y.; Yu, J.; Zhang, D. *N,N'*-Bisaryl Substituted Chiral Linker-Bridged Bis(*N*-Heterocyclic Carbene) Palladium Complexes: Design, Synthesis, and Catalytic Properties. *Organometallics* **2017**, *36*, 1372−1382.

(8) For selected reviews of palladium-NHC catalysts, see: (a) Herrmann, W. A. *N*-Heterocyclic Carbenes: A New Concept in Organometallic Catalysis. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290−1309. (b) Díez-Gonzàlez, S.; Marion, N.; Nolan, S. P. *N*-Heterocyclic Carbenes in Late Transition Metal Catalysis. *Chem. Rev.* **2009**, *109*, 3612−3676. (c) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. Palladium Complexes of *N*-Heterocyclic Carbenes as Catalysts for Cross-Coupling Reactions − A Synthetic Chemist's Perspective. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768−2813. (d) Fortman, G. C.; Nolan, S. P. *N*-Heterocyclic carbene (NHC) ligands and palladium in homogeneous cross-coupling catalysis: a perfect union. *Chem. Soc. Rev.* **2011**, *40*, 5151−5169.

(9) For selected reviews of chiral palladium-NHC catalysts, see: (a) Perry, M. C.; Burgess, K. Chiral *N*-Heterocyclic Carbene-Transition Metal Complexes in Asymmetric Catalysis. *Tetrahedron: Asymmetry* **2003**, *14*, 951−961. (b) César, V.; Bellemin-Laponnaz, S.; Gade, L. H. Chiral *N*-Heterocyclic Carbenes as Stereodirecting Ligands in Asymmetric Catalysis. *Chem. Soc. Rev.* **2004**, *33*, 619−636. (c) Wang, F.; Liu, L.-j.; Wang, W.; Li, S.; Shi, M. Chiral NHC-Metal-Based Asymmetric Catalysis. *Coord. Chem. Rev.* **2012**, *256*, 804−853. (d) Zhao, D.; Candish, L.; Paul, D.; Glorius, F. *N*-Heterocyclic Carbenes in Asymmetric Hydrogenation. *ACS Catal.* **2016**, *6*, 5978−5988. (e) Janssen-Müller, D.; Schlepphorst, C.; Glorius, F. Privileged Chiral N-Heterocyclic Carbene Ligands for Asymmetric Transition-Metal Catalysis. *Chem. Soc. Rev.* **2017**, *46*, 4845−4854.

(10) Zhang, D.; Yu, J. Palladium Complexes Bearing Chiral bis(NHC) Chelating Ligands on a Spiro Scaffold: Synthesis, Characterization, and Their Application in the Oxidative Kinetic Resolution of Secondary Alcohols. *Organometallics* **2020**, *39*, 605−613.

(11) Liu, Z.; Zhang, T.; Shi, M. Cyclometalated cis-Chelated Bidentate N-Heterocyclic Carbene Palladium Complexes: Synthetic, Structural, and Catalytic Studies. *Organometallics* **2008**, *27*, 2668−2671.

(12) (a) Rani, V.; Singh, H. B.; Butcher, R. J. Cationic NCN Palladium(II) Pincer Complexes of 5-tert-Butyl-1,3-bis(N-substituted benzimidazol-2-yl)benzenes: Synthesis, Structure, and Pd···Pd Metallophilic Interaction. *Organometallics* **2017**, *36*, 4741−4752. (b) Santana, M. D.; Garcia-Bueno, R.; Garcia, G.; Sanchez, G.; Garcia, J.; Kapdi, A. R.; Naik, M.; Pednekar, S.; Perez, J.; Garcia, L.; Perez, E.; Serrano, J. L. Novel saccharinate-bridged palladium complexes for efficient C−O bond activation displaying promising luminescence properties. *Dalton Trans.* **2012**, *41*, 3832−3842. (c) Karami, K.; Alinaghi, M.; Amirghofran, Z.; Lipkowskic, J.; Momtazi-Borojenide, A. A. A saccharinate-bridged palladacyclic dimer with a Pd−Pd bond: experimental and molecular docking studies of the interaction with DNA and BSA and in vitro cytotoxicity against human cancer cell lines. *New J. Chem.* **2018**, *42*, 574−586. (d) Campbell, M. G.; Zheng, S.-L.; Ritter, T. One-Dimensional Palladium Wires: Influence of Molecular Changes on Supramolecular Structure. *Inorg. Chem.* **2013**, *52*, 13295−13297.

(13) Mikami, K.; Miyamoto, T.; Hatano, M. A highly efficient asymmetric Suzuki−Miyaura coupling reaction catalyzed by cationic chiral palladium(ii) complexes. *Chem. Commun.* **2004**, 2082−2083.

(14) Sheldrick, G. M. *SHELXL-97, Program for the Refinement of Crystal Structures*; Universität Göttingen: Göttingen, Germany, 1997.

https://dx.doi.org/10.1021/acs.organomet.0c00036
Organometallics XXXX, XXX, XXX−XXX