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Pyridine–hydrazone ligands in enantioselective palladium–catalyzed Suzuki-Miyaura cross–couplings

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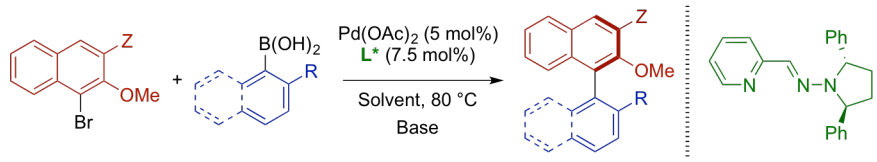

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Tetrahedron

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Pyridine–hydrazone ligands in enantioselective palladium-catalyzed Suzuki-Miyaura cross–couplings

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The geometries and coordination properties of modular pyridine–hydrazone N,N-ligands containing C_2-symmetric *trans*-2,5-diphenylpyrrolidine and *trans*-2,5-diphenylpiperidine as the terminal dialkylamino units have been analyzed by X-ray diffraction analysis of $[PdCl_2(N,N)]$ complexes [(N,N) = pyridine hydrazone ligand]. In combination with $Pd(OAc)_2$ as the precatalyst, these ligands provide high enantioselectivities (up to 95:5 er) in asymmetric Suzuki-Miyaura cross couplings of 2-methoxy-1-naphthyl bromides with 1-naphthyl and 2-tolyl boronic acids.

Keywords:
Cross-coupling
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Asymmetric Catalysis
Palladium
Biaryls

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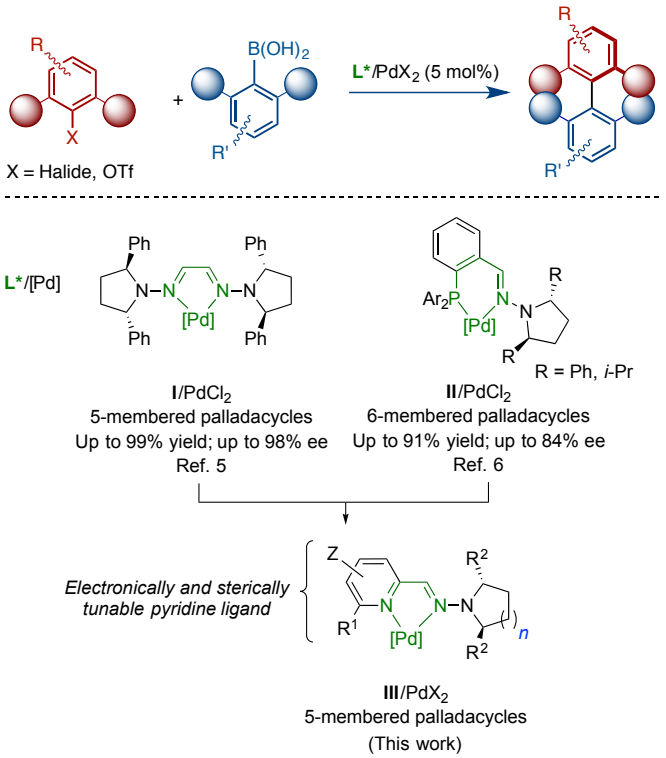
1. Introduction

Palladium catalyzed asymmetric Suzuki-Miyaura cross coupling is one of the most useful C-C bond forming reactions for the synthesis of axially chiral biaryl compounds.[1] Since seminal communications by Buchwald[2] and Cammidge[3] relatively few catalytic systems enabling efficient control of axial chirality in biaryls synthesis have been described. To date, most of the successful examples are based on palladium complexes containing chiral phosphine ligands [mono-phosphine (P), bi-phosphine (P,P) and heterobidentate P,X ligands (X = O or N)]. The most recent studies include also the use of phosphine-free dienes[4] and N-heterocyclic carbenes.[5] On the other hand, based in previous results by Nolan[6] and Mino,[7] we reported on the use of electron–rich glyoxal bis-hydrazone **I** (Scheme 1) as a phosphine–free ligand in this reaction. This type of ligand class, had been previosly used in asymmetric Cu(II)–catalyzed Diels-Alder cycloadditions,[8] exhibiting a high level of enantiocontrol based on a related square–planar geometry. In fact, the use of **I**/$PdCl_2$ complex as the precatalyst enabled the obtention of a series of biaryls, particularly unfunctionalized binaphtalenes, with unprecedented enantioselectivities at low temperatures.[9]

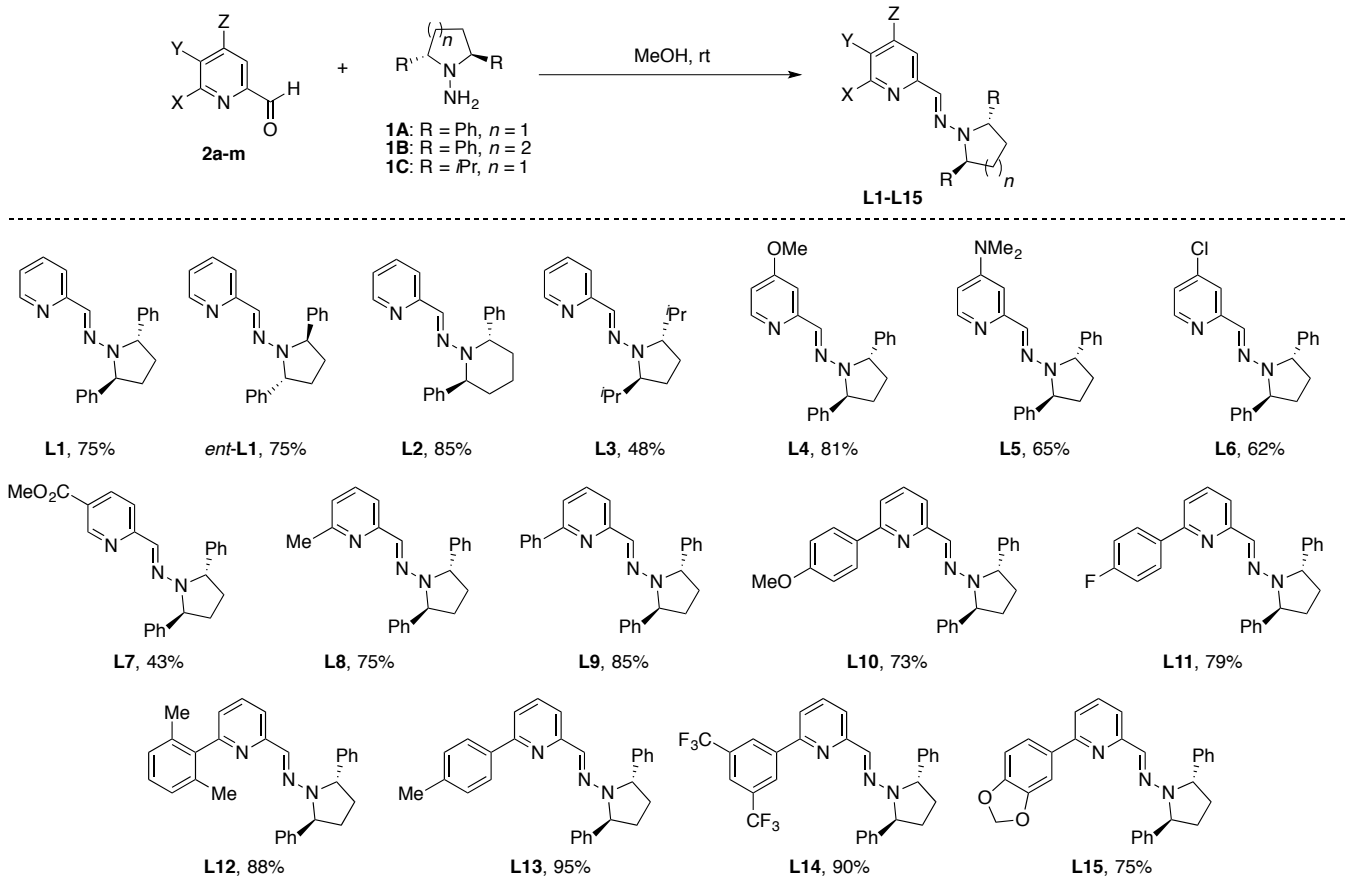


Scheme 1. Hydrazone based ligands in the asymmetric Suzuki-Miyaura reaction.

The high efficiency of **I**/$PdCl_2$ system was associated with the intrinsic features of the ligand **I**: (a) C_2 symmetry of the terminal dialkylamino group (2,5-diphenylpyrrolidino). This property makes the rotation arond N–N bonds inconsequential (maintaining a suitable chiral environment in the proximity of the Pd center) and proved to be essential for reaching high enantioselectivities; (b) limited flexibility arounds the conjugated C=N-N system, providing an adequate chiral environment for square-planar 5-membered palladacycles; (c) a considerable steric crowding for the stabilization of the intermediate Pd(0) species, (d) a relatively high electron density ($n\rightarrow\pi$ conjugation) in the system which normally favor the oxidative addition step and finally (e) the potential hemilabile behavior which might be essential for the transmetalation event, as recently outlined by Denmark and Houk.[10]

In spite of the excellent results achieved with ligand **I**, there are still limitations related with the lower enantioselectivities achieved with electron poor electrophiles and the long reaction times required in some cases for reaction completion. In an attempt to overcome these limitations, the original design was later extended to 6-membered palladacyclic complexes containing phosphino-hydrazone P,N ligands **II** which, interestingly, exhibited excellent catalytic activities and good stereocontrol with complementary families of substrates.[11]

Aiming to expand the strategy of combining a C_2–symmetric hydrazone ligand with a different highly-tunable coordinating functionality we have recently developed a new family of heterofunctional N,N´ pyridine–hydrazone ligands **III**, which have been succesfully tested in Pd(II)-catalyzed arylations of cyclic sulphonylketimines[12] and Ru(II)-catalyzed decarboxylative allylic etherification reactions.[13] In this paper, we present new palladium complexes based on pyridine–hydrazone ligands **III** (forming 5-membered palladacycles), their structural analysis and their use in asymmetric Suzuki-Miyaura reactions.

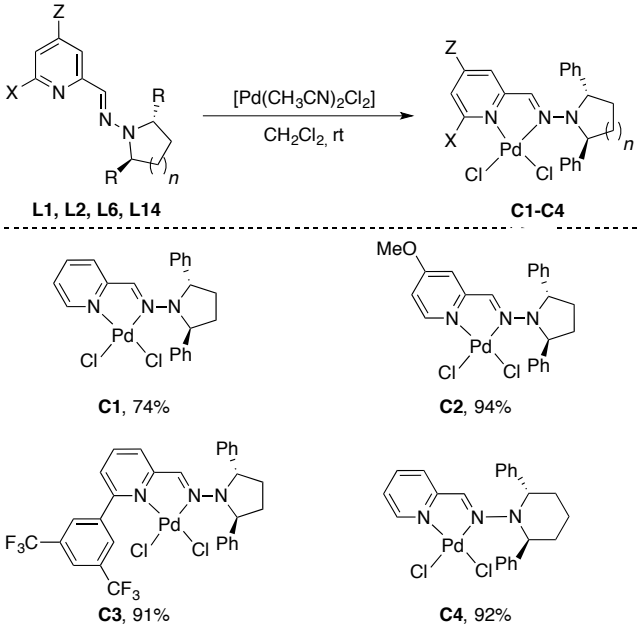


Scheme 2. Synthesis of pyridine–hydrazone ligands **L1-L15**

2. Results and discussion

2.1. Synthesis of ligands and Palladium (II) complexes

A first set of the suggested pyridine–hydrazone ligands **L1-L15** were synthesized in 43-95% yield by simple condensation of a variety of readily available 2-formylpyridines **2** with different substitution patterns and C_2–symmetric hydrazines such as (2*S*,5*S*)-1-amino-2,5-diphenylpyrrolidine (**1A**),[8] (2*R*,5*R*)-1-amino-2,5-diphenyl-pyrrolidine (*ent*-**1A**),[8] (2*S*,6*S*)-1-amino-2,6-diphenylpiperidine (**1B**),[8] and (2*S*,5*S*)-1-amino-2,5-diisopropylpyrrolidine (**1C**)[11] (Scheme 2). Reactions of representative pyridine–hydrazone ligands **L1**, **L2**, **L6** and **L14** with $[PdCl_2(CH_3CN)_2]$ in dry CH_2Cl_2 at room temperature afforded the corresponding $[PdCl_2(N,N)]$ neutral complexes **C1-C4** in 74-94% yields (Scheme 3). The complexes were characterized in solution by ^1H and ^{13}C NMR spectroscopy. Additionally, good quality crystals of these complexes could be grown by slow difussion of *n*-hexane into a solution of the complexes in CH_2Cl_2. Therefore, their solid state structural analysis was also performed by single–crystal X-ray diffraction, to obtain valuable information about the coordination features and geometries of pyridine–hydrazone ligands.



Scheme 3. Synthesis of Pd(II) complexes **C1-C4**

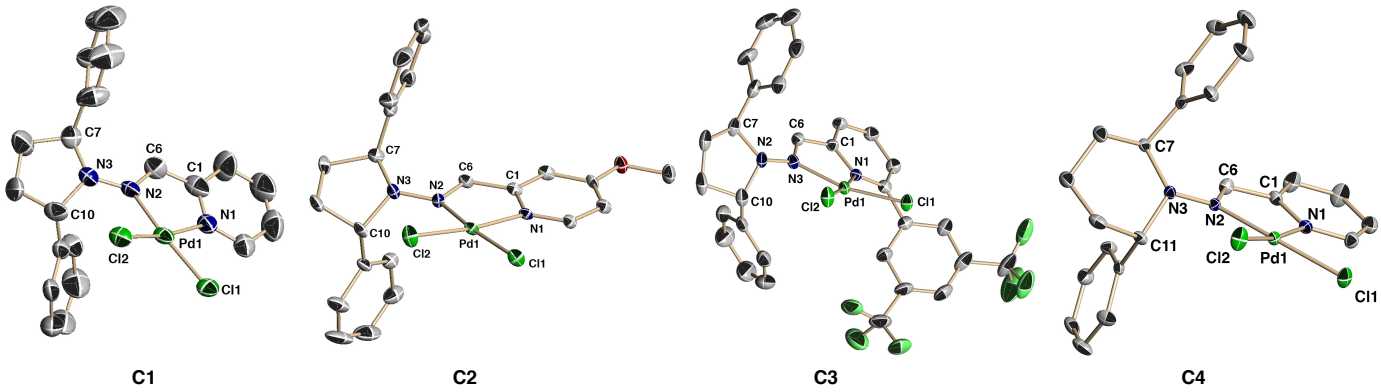


Figure 1. ORTEP drawings of complexes **C1-C4:** Thermal ellipsoids are drawn at the 30% probability level. Hydrogen atoms are omitted for clarity. The structure shown for **C1** corresponds to one out of three independent molecules in the molecular cell. The structure shown for **C2** corresponds to one out of two independent molecules in the molecular cell. Selected crystallographic data for all structures are colleted in Table 1.

Table 1. Selected bond lengths (Å) and bond angles (deg) for complexes **C1-C4** shown in Figure 1

Structure	**C1**(M1)	**C1**(M2)	**C1**(M3)	**C2**(M1)	**C2**(M2)	**C3**	**C4**
Square planar distortion (deg)	11.5	6.3	8.3	6.2	5.3	**12.8**	8.0
Angle between ligand and coordination planes (deg)	21.0	12.5	19.4	12.5	11.3	**29.6**	12.0
Virtual angle N2-N3-C7-C10/11 (deg)	151.0	149.4	159.3	149.0	150.4	144.5	143.8
$\sqrt{(360-\Sigma)}$	2.67	2.74	1.87	2.76	2.60	3.12	3.06
Dihedral C=N-N-C (deg)	-5.4(12)	-15.1(12)	-13.0(12)	-10.3(9)	-22.9(10)	-12.2(5)	-21.7(5)
Pd–N(Py) (Å)	2.013(8)	2.017(5)	1.989(8)	2.036(6)	2.016(6)	2.050(3)	2.035(4)
Pd–N(Hyd) (Å)	2.049(7)	2.047(6)	2.075(7	2.084(6)	2.073(6)	2.043(3)	2.041(4)
Pd–Cl (trans to Py) (Å)	2.283(2)	2.2769(17)	2.286(3)	2.278(2)	2.289(2)	2.2937(9)	2.2825(12)
Pd–Cl (trans to Hyd) (Å)	2.284(2)	2.2734(19)	2.271(3)	2.2874(19)	2.293(2)	2.2826(9)	2.2799(13)

2.2. Structural analysis

The solid state structure of diphenylpirrolidine(or piperidine) derivatives **C1-C4**[14] reveals the expected square-planar geometry around the palladium center, although a slight distortion was observed in all cases. This distortion, presumably caused by the steric repulsion with the bulky 2,5-diphenylpyrrolidino(piperidino) group, has been measured as the torsion angle between the planes defined by N(2)−Pd−N(1) and Cl(1)−Pd−Cl(2), respectively, reaching low to moderate values (5.3–11.5 deg) in most cases (Table 1). In the case of **C3**, however, the presence of the additional aromatic ring at C(6) originates a steric repulsion between the chlorine atom *trans* to the hydrazone N(sp^2) and the 3,5-$(CF_3)_2$-C_6H_3 group, forcing a slightly higher deviation from the square planar geometry (torsion angle 12.8 deg).

As one of the remarkable characteristics, the structures of **C1-C4** show a relatively low deviation of coplanarity between ligand plane (defined as the plane fitting through N(1)-C(1)-C(6)-N(2) and the coordination plane (defined as the plane fitting through N(1)-N(2)-Pd-Cl(1)-Cl-(2). Again, the presence of an aryl group at position C(6) makes this deviation more significant in **C3** (angle between planes 29.6 deg). Nevertheless, there is a sharp contrast between these geometries and those of related phosphino–hydrazone complexes **II**/[Pd][11,15] which, having six–membered geometries, are characterized by a much larger deviation angle (54.1 to 62.6). Interestingly, this comparison reveals also that phosphino–hydrazone ligands regularly exhibit a more efficient $n\rightarrow\pi$ conjugation in the hydrazone system. Thus, the pyramidalization degree, measured either as the virtual dihedral angle N(2)-N(3)-C(7)-C(10)[16] or using the $\sqrt{(360-\Sigma)}$ descriptor,[17] is regularly lower in phosphino-hydrazone complexes than in complexes **C1-C4**. Thus, the average virtual angle in **II**/$PdCl_2$ complexes[11] is 161.7 deg, while the average value for comparable pyrrolidine derivatives **C1-C3** is 150.6 deg. Additionally, the average values for the $\sqrt{(360-\Sigma}$ descriptor is 1.49 for **II**/$PdCl_2$ complexes, much lower than the corresponding average values of 2.26 calculated for **C1-C3**. Not surprisingly, the largest value of 3.12 was observed in the sterically distorted complex **C3**. The planarity degree in the 2,6-diphenylpiperidine derivative **C4** (not included in the above discussed comparison), is also relatively low (virtual angle = 143.8 deg; $\sqrt{(360-\Sigma}$ = 3.06) as expected for the lower tendency of the piperidine N(sp^3) atom to reach planar conformations.

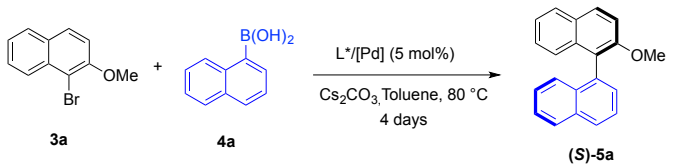
The structures show also typical Pd–N distances, being the Pd–N(Py) bond (average 2.02 Å) shorter in general than the Pd–N(Hyd) one (average 2.06 Å), which is in accordance with the higher basicity of the pyridine fragment. Unexpectedly, though, the Pd–Cl(1) and Pd–Cl(2) bond distances are very similar in all cases, not reflecting a significant *trans* influence by any of the N atoms. This is in sharp contrast with the previously reported allyl complex,[12] in which the Pd−C bond *trans* to the pyridine N is significantly longer [2.150(5) Å] compared to the Pd−C bond *trans* to the hydrazone N [2.099(5) Å], reflecting in this case the higher *trans* influence of the more basic pyridine nitrogen.

2.3. Asymmetric Suzuki-Miyaura cross-coupling

Complexes prepared *in situ* from **L1-L15** and $[PdCl_2(CH_3CN)_2]$ were then tested in the asymmetric Suzuki–Miyaura cross-coupling reaction between 1-bromo-2-methoxynaphthalene (**3a**) and 1-naphthyl boronic acid (**4a**) (Table 2). The reactions carried out at 80 °C for 4 days employing **L1-L3**/$PdCl_2$ as precatalyst, Cs_2CO_3 as the base and toluene as the solvent, afforded (*S*)-2-methoxy-1,1'-binaphthyl [(*S*)-**5a**] in moderate conversions (50-65%) and enantioselectivities (63:37-85:15 er) (entries 1-3). The analysis of these results indicates that the pyrrolidine-derived **L1** provides a better chiral environment than the piperidine-derived **L2**, a fact that has been repeteadly obverved in related catalsyts[8,9,11,12] and that is presumably related with the higher conformational flexibility of the piperidine moiety, in turn associated with the weaker $n\rightarrow\pi$ conjugation. 2,5-Diisopropylpyrrolidine derivative **L3**, lacking possible preferred orientations of aryl groups in oxidative addition intermediates due to stabilizing π-π interactions, was also less efficient. Next, it was explored the influence of substituents on the pyridine moiety. The presence of electron-donating [4-MeO, **L4** and 4-NMe_2, **L5**] and electron-withdrawing [4-Cl, **L6** and 5-CO_2Me, **L7**] groups had a detrimental effect on catalytic activities (entries 4-7), affording (*S*)-**5a** in lower conversions (35-50%) and similar enantioselectivities. The effect of the steric properties of ligands containing substituents at C-6 of the pyridine ring (**L8-L15**) was subsequently investigated. Methyl- substituted ligand **L8** gave a similar level of conversion and slightly lower enantioselectivity (80:20 er, entry 8). The introduction of aryl groups at C(6) in ligands **L9-L15** had also a negative effect on the performance of the catalyst**,** affording (*S*)-**5a** in moderate (50-65%, entries 9, 11 and 13) to good conversions (82->95%, entries 10, 12, 14 and 15), albeit lower enantioselectivities (up to 68:32 er for **L10** and **L11**). It is worth mentioning that enantioinversion was observed with the ligand **L14** (entry 14), and the coupling product (*R*)-**5a** was obtained in full conversion and 35:65 er. Finally, reactions carried out with preformed complexes **C1-C4** afforded the same level of enantioselectivity and similar conversions than those accomplished with *in situ* formed precatalysts.

Having identified the simplest **L1** as the most selective ligand, experiments with different Pd sources were conducted. Surprisingly, Pd(0) precursors [$Pd(dba)_2$ and $Pd_2(dba)_3$] showed no catalytic activity (<5% conversion after 4 days), while Pd(II) sources containing less coordinating anions such as $Pd(OAc)_2$ afforded (*S*)-**5a** in 54% conversion and an improved 95:5 er. (Table 3, entry 1). A screening of different bases (entries 2-5) and solvents (entries 6-9) revealed CsF in toluene as a good alternative to Cs_2CO_3, reaching 71% conversion and 94:6 er (entry 5 vs 1), although the reaction time remained relatively long (96 h). Finally, reactions were made in Toluene/H_2O mixtures, being 9:1 the optimal ratio (entries 10 and 11). To our delight, this solvent combination had a positive effect on the catalytic activity, possibly associated with solubility issues, and afforded high conversions (>95%) and still good enantioselectivities. Remarkably, employing Cs_2CO_3 as the base

Table 2. Pd-catalyzed asymmetric Suzuki-Miyaura reactions: ligand screening[a]

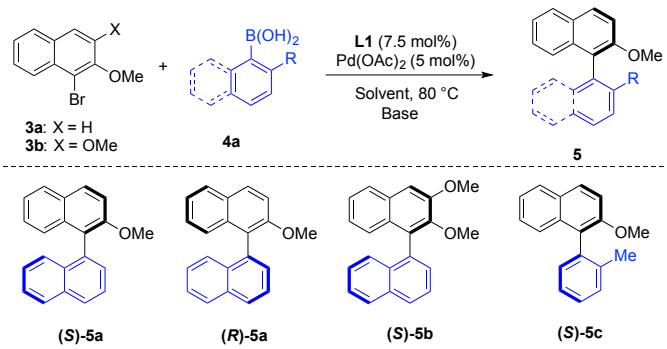


3a **4a** **(*S*)-5a**

entry	Precatalyst[b]	Conv. (%)[c]	er (*S*:*R*)[d]
1	**L1/[Pd]**	**65**	**85:15**
2	**L2**/[Pd]	60	78:22
3	**L3**/[Pd]	50	63:37
4	**L4**/[Pd]	36	84:16
5	**L5**/[Pd]	35	82:18
6	**L6**/[Pd]	55	84:16
7	**L7**/[Pd]	50	84:16
8	**L8**/[Pd]	60	80:20
9	**L9**/[Pd]	50	59:41
10	**L10**/[Pd]	>95	68:32
11	**L11**/[Pd]	62	68:32
12	**L12**/[Pd]	>95	58:42
13	**L13**/[Pd]	65	61:39
14	**L14**/[Pd]	85	35:65
15	**L15**/[Pd]	82	56:44
16	**C1**	**70**	**84:16**
17	**C2**	60	84:16
18	**C3**	90	35:65
19	**C4**	67	78:22

[a] Reactions were carried at 0.1 mmol scale. [b] [Pd] = $PdCl_2(CH_3CN)_2$. [c] Determined by ^{1}H-NMR. [d] Determined by HPLC using chiral columns.

Table 3. Pd-catalyzed asymmetric Suzuki-Miyaura reactions: reaction optimization and scope[a]



(*S*)-5a **(*R*)-5a** **(*S*)-5b** **(*S*)-5c**

entry	Base	Solvent	*t* (h)	**5**, Conv. (%)[b]	er (*S*:*R*)[c]
1	Cs_2CO_3	Toluene	96	(*S*)-**5a**, 54	95:5
2	^{t}BuOK	Toluene	96	(*S*)-**5a**, 16	91:9
3	$Ba(OH)_2$	Toluene	96	(*S*)-**5a**, 40	84:16
4	K_3PO_4	Toluene	96	(*S*)-**5a**, 44	90:10
5	CsF	Toluene	96	(*S*)-**5a**, 71	94:6
6	Cs_2CO_3	DCE	96	(*S*)-**5a**, 26	93:7
7	Cs_2CO_3	Dioxane	96	(*S*)-**5a**, 60	91:9
8	Cs_2CO_3	MeOH	96	(*S*)-**5a**, 32	92:8
9	Cs_2CO_3	H_2O	96	(*S*)-**5a**, 42	75:25
10[d]	Cs_2CO_3	Toluene/H_2O, 9/1	15	(*S*)-**5a**, >95 (99)	94:6
11	CsF	Toluene/H_2O, 9/1	96	(*S*)-**5a**, 93	93:7
12[d,e]	Cs_2CO_3	Toluene/H_2O, 9/1	15	(*R*)-**5a,** >95 (99)	9:91
13[d]	Cs_2CO_3	Toluene/H_2O, 9/1	48	(*S*)-**5b,** >95 (99)	94:6
14[d]	Cs_2CO_3	Toluene/H_2O, 9/1	96	(*S*)-**5c,** >95 (99)	84:16

[a] Reactions were carried at 0.1 mmol scale. [b] Isolated yield are given in brackets. [c] Determined by HPLC using chiral stationary phases. [d] Reactions were carried at 0.2 mmol scale. [e] Employing *ent*-**L1**.

the reaction took place in 15 hours, yielding (*S*)-**5a** in quantitative yield and 94:6 er (entry 10). Unfortunately the enantioselectivity could not be further improved at lower temperatures. The opposite (*R*)-**5a** enantiomer was obtained applying ***ent*-L1** (entry 12), thereby highlighting the availability of both enantiomers of the ligand.

Under optimized conditions, other biaryl compounds (*S*)-**5b** and (*S*)-**5c** were synthesized in quantitative yields and enantioselectivities from good (94:6 er for (*S*)-**5b**, entry 13) to moderate (84:16 er for (*S*)-**5c**, entry 14), albeit in longer reaction times (48 and 96 hours, respectively).

3. Conclusion

In summary, pyridine–hydrazone ligands form neutral five-membered Pd(II) complexes showing geometries that exhibit significant differences with those previously found in related six-membered phosphino–hydrazones. Under optimized conditions, these complexes behave as efficient catalysts for the asymmetric Suzuki–Miyaura cross–coupling of 2-methoxy-1-naphthyl bromides with 1-naphthyl and 2-tolyl boronic acids. Together with the results collected in the asymmetric 1,2–addition of boronic acids to cyclic sulphonylketimines[12] and Ru(II)-catalyzed decarboxylative allylic etherification reactions,[13] these results suggest that this type of ligands is an interesting alternative to better established chiral N,N ligands such as bis–oxazolines or pyridine–oxazolines.

4. Experimental Section

General experimental methods. ^{1}H NMR spectra were recorded at 300 MHz, 400 MHz or 500 MHz; ^{13}C NMR spectra were recorded at 75 MHz, 100 MHz or 125 MHz, with the solvent peak used as the internal reference. Flash chromatography was carried out on silica-gel (40-63 μm or 15-40 μm). Melting points were recorded in a metal block and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 MC polarimeter. The enantiomeric excesses (ee) were measured by HPLC on chiral stationary phase with ^{i}PrOH/*n*-hexane mixtures as the eluents. Solvents were purified and dried by standard procedures. 6-bromo-2-formylpyridine, 2-formylpyridine (**2a**), 6-methyl-2-formylpyridine (**2f**), 6-(4-fluorophenyl)-2-formylpyridine (**2i**), 6-(benzo[*d*][1,3]dioxol-5-yl)-2-formylpyridine (**2m**), $[Pd(CH_3CN)_2Cl_2]$, 1-bromo-2-methoxynaphthalene (**3a**), 1-bromo-2,3-dimethoxynaphthalene (**3b**), 1-naphthylboronic acid (**4a**) and 2-tolylboronic acid (**4b**) were purchased from Aldrich and used as received. (2*S*,5*S*)-1-Amino-2,5-diphenylpyrrolidine (**1A**),[8] (2*R*,5*R*)-1-amino-2,5-diphenylpyrrolidine (*ent*-**1A**),[8] (2*S*,6*S*)-1-amino-2,6-diphenylpiperidine (**1B**),[8] (2*S*,5*S*)-1-amino-2,5-diisopropylpyrrolidine (**1C**),[11] pyridine aldehydes **2b,d**[18] **2c**,[19] and **2e**,[20] and pyridine–hydrazones **L1-L8**[12] were prepared according to the literature procedures.

General Procedure for the synthesis of pyridine–aldehydes 2: 6-Bromo-2-formylpyridine (5.4 mmol, 1.0 g) was added to a solution of $Pd(PPh_3)_4$ (3 mol%, 186 mg) in deoxygenated DME (10 mL), under Argon. After 10 min, stirring at rt, the corresponding boronic acid (7.5 mmol) and a Na_2CO_3 (2M aq., 5.5 mL) solution were added and the reaction mixture was stirred at 90 °C for 16 h. H_2O was added and the layers were separated. The aqueous portion was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organics were dried, concentrated and the resulting residue was purified by flash chromatography. Yields and characterization data for compounds **2** are as follows:

6-Phenylpicolinaldehyde (2g). Following the general procedure using phenyl boronic acid (7.5 mmol, 919 mg), flash chromatography (EtOAc:hexane 1:30) gave **2g** (772 mg, 78%) as a yellow solid. M.P. = 68-69 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.18 (s, 1H), 8.11-8.09 (m, 2H), 7.98-7.90 (m, 3H), 7.56-7.48 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.9, 158.0, 152.8, 138.2, 137.8, 129.7, 128.9, 127.0, 124.4, 119.8. HRMS (CI) *m/z* calcd for $C_{12}H_9NO$ 183.0684, found 183.0687.

6-(2,6-Dimethylphenyl)picolinaldehyde (2j). Following the general procedure using 2,6-dimethylphenyl boronic acid (7.5 mmol, 1.13 g), flash chromatography (EtOAc:hexane 1:15) gave **2j** (1.0 g, 97%) as a white solid. M.P. = 75-77 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.12 (s, 1H), 7.96 (d, 2H, J = 7.5 Hz), 7.49-7.47 (m, 1H), 7.24 (t, 1H, J = 7.8 Hz), 7.14 (d, 2H, J = 7.8 Hz), 2.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 160.7, 152.8, 139.2, 137.4, 135.7, 128.9, 128.4, 127.8, 119.6, 20.2. HRMS (CI) *m/z* calcd for $C_{14}H_{13}NO$ 211.0997, found 211.0997.

6-(4-(Tert-butyl)phenyl)picolinaldehyde (2k). Following the general procedure using 4-(*tert*-butyl)phenyl boronic acid (7.5 mmol, 1.34 g), flash chromatography (EtOAc:hexane 1:8) gave **2k** (1.12 g, 87%) as a yellow solid. M.P. = 78-80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.17 (s, 1H), 8.04-8.00 (m, 2H), 7.93-7.88 (m, 3H), 7.56-7.53 (m, 2H), 1.38 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.0, 158.0, 153.0, 152.7, 137.6, 135.4, 126.7, 125.9, 124.2, 119.4, 34.7, 31.2. HRMS (CI) *m/z* calcd for $C_{16}H_{17}NO$ 239.1310, found 239.1318.

6-(3,5-Bis(trifluoromethyl)phenyl)picolinaldehyde (2l). Following the general procedure using 3,5-bis(trifluoromethyl)-phenyl boronic acid (7.5 mmol, 1.94 g), flash chromatography (EtOAc:hexane 1:8) gave **2l** (1.16 g, 71%) as a yellow solid. M.P. = 92-93 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.2 (s, 1H), 8.58 (s, 2H), 8.08-7.98 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.2, 154.5, 153.1, 140.1, 138.5, 132.5 (q, $J_{C\text{-}F}$ = 33 Hz), 127.1, 127.0, 124.4, 123.3 (q, $J_{C\text{-}F}$ = 271 Hz), 121.2. HRMS (CI) *m/z* calcd for $C_{14}H_7NOF_6$ 319.0432, found 319.0437.

General procedure for the synthesis of pyridine–hydrazones L9-L15: A solution of the corresponding aldehyde **2** (1 mmol) in MeOH (1 mL) was dropwise added to a solution of (2*S*,5*S*)-1-amino-2,5-diphenylpyrrolidine **1a** (1.1 mmol, 263 mg) in MeOH (1 mL). The reaction mixture was stirred at rt for 3 hours. A partial precipitation of the product was observed and the formed pyridine–hydrazone was filtered, and the mother liquor containing product was concentrated to dryness and purified by flash chromatography. Yields and characterization data for compounds **L9-L15** are as follows:

Pyridine-hydrazone (L9). Following the general procedure, flash chromatography (EtOAc:*n*-hexane 1:20, 1% Et_3N) gave **L9** (342 mg, 85%) as a yellow-orange foam. $[\alpha]^{20}_D$ –259.5 (*c* 0.54, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (m, 2H), 7.62-7.22 (m, 16H), 7.09 (s, 1H), 5.23 (d, 2H, J = 6.8 Hz), 2.59-2.52 (m, 2H), 1.91-1.81 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.5, 156.4, 143.0, 139.8, 136.3, 132.3, 128.6, 128.5, 128.4, 126.9, 126.8, 126.2, 117.9, 116.8, 65.2, 31.4. HRMS (CI) *m/z* calcd for $C_{28}H_{25}N_3$ 403.2048, found 403.2061.

Pyridine-hydrazone (L10). Following the general procedure, flash chromatography (Et_2O:*n*-hexane 1:8→1:4, 1% Et_3N) gave **L10** (314 mg, 73%) as a white solid. M.P. = 112-113 °C. $[\alpha]^{20}_D$ – 310.2 (*c* 0.83, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, 2H, *J* = 8.8 Hz), 7.56-7.42 (m, 2H), 7.40-7.19 (m, 11H), 7.10 (s, 1H), 6.93 (d, 2H, *J* = 8.8 Hz), 5.23 (d, 2H, *J* = 6.7 Hz), 3.82 (s, 3H), 2.70-2.45 (m, 2H), 1.95-1.75 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 156.3, 156.1, 143.0, 136.3, 132.5, 132.4, 128.5, 128.1, 126.8, 126.2, 117.2, 116.1, 113.9, 65.2, 55.3, 31.5. HRMS (CI) *m/z* calcd for $C_{29}H_{28}N_3O$ 434.2232 (M^+ + 1), found 434.2234.

Pyridine-hydrazone (L11). Following the general procedure, flash chromatography (toluene:*n*-hexane 1:1→2:1, 1% Et_3N) gave **L11** (334 mg, 79%) as a yellow solid. M.P. = 115-117 °C. $[\alpha]^{20}_D$ –58.8 (*c* 0.90, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.88-7.81 (m, 2H), 7.54 (dd, 1H, J = 7.9, 0.9 Hz), 7.47 (t, 1H, J = 7.9 Hz), 7.38-7.32 (m, 4H), 7.30 (dd, 1H, J = 7.9, 0.9 Hz), 7.28-7.21 (m, 6H), 7.12-7.04 (m, 3H), 5.24 (d, *J* = 7.0 Hz), 2.62-2.49 (m, 2H), 1.97-1.78 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.3 (q, *J* = 249.0 Hz), 156.4, 155.3, 142.9, 136.4, 132.0, 128.7, 128.6, 126.9 (q, *J* = 7.8 Hz), 126.6, 126.2, 117.5, 116.7, 115.4 (q, *J* = 23.2 Hz), 65.3, 31.6 HRMS (CI) *m/z* calcd for $C_{28}H_{25}N_3F$ (M^+ + 1) 422.2028, found 422.2033.

Pyridine-hydrazone (L12). Following the general procedure, flash chromatography (toluene, 1% Et_3N) gave **L12** (352 mg, 88%) as a yellow foam. $[\alpha]^{20}_D$ –330.9 (*c* 0.80, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.58 (dd, 1H, *J* = 8.1, 2.0 Hz), 7.50 (t, 1H, *J* = 7.4 Hz), 7.36-7.33 (m, 4H), 7.26-7.24 (m, 6H), 7.14-7.10 (m, 1H), 7.06-7.00 (m, 3H), 7.03 (s, 1H), 6.88 (dd, 1H, *J* = 7.4, 1.1 Hz), 5.22 (d, 2H, *J* = 7.0 Hz), 2.60-2.51 (m, 2H), 1.99 (s, 6H), 1.90-1.84 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.6, 156.5, 142.8, 140.6, 135.9, 135.8, 132.2, 128.5, 127.6, 127.5, 126.8, 126.3, 121.5, 116.1, 65.2, 31.4, 20.2. HRMS (CI) *m/z* calcd for $C_{30}H_{30}N_3$ 432.2440 (M^+ + 1), found 432.2435.

Pyridine-hydrazone (L13). Following the general procedure, flash chromatography (EtOAc:*n*-hexano 1:20, 1% Et_3N) gave **L13** (437 mg, 95%) as a yellow foam. $[\alpha]^{20}_D$ –256.8 (*c* 0.62, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.81-7.77 (m, 2H), 7.57-7.23 (m, 15H), 7.11 (s, 1H), 5.25 (dd, 2H, *J* = 6.8, 1.2 Hz), 2.59-2.51 (m, 2H), 1.91-1.80 (m, 2H), 1.33 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.6, 156.3, 151.5, 143.0, 137.1, 136.2, 132.5, 128.6, 128.5, 126.8, 126.6, 126.2, 125.5, 116.4, 65.2, 34.6, 31.4, 31.2. HRMS (CI) *m/z* calcd for $C_{32}H_{33}N_3$ 459.2674, found 459.2662.

Pyridine-hydrazone (L14). Following the general procedure, flash chromatography (toluene:*n*-hexane 1:2, 1% Et_3N) gave **L14** (486 mg, 90%) as a yellow solid. M.P. = 122-124 °C. $[\alpha]^{20}_D$ – 229.2 (*c* 0.80, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.34 (s, 2H), 7.84 (s, 1H), 7.68-7.25 (m, 13H), 7.07 (s, 1H), 5.25 (d, 2H, *J* = 6.7 Hz), 2.61-2.55 (m, 2H), 1.94-1.84 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.1, 153.1, 142.8, 141.7, 136.8, 132.3 (q, $J_{C\text{-}F}$ = 34.0 Hz), 131.4, 128.7, 127.1, 127.0, 126.9, 126.3, 122.3 (q, $J_{C\text{-}F}$ = 272.0 Hz), 122.1, 118.4, 117.9, 65.4, 31.6. HRMS (CI) *m/z* calcd for $C_{30}H_{24}N_3F_6$ 540.1874 (M^+ + 1), found 540.1882.

Pyridine-hydrazone (L15). Following the general procedure, flash chromatography (EtOAc:*n*-hexane 1:8, 1% Et_3N) gave **L15** (334 mg, 75%) as a white solid. M.P. = 137-138 °C. $[\alpha]^{20}_D$ – 260.9 (*c* 0.90, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.52-7.23 (m, 15H), 7.07 (s, 1H), 6.82 (d, 1H, *J* = 8.1 Hz), 5.94 (s, 2H), 5.23 (d, 2H, *J* = 6.7 Hz), 2.58-2.53 (m, 2H), 1.87-1.85 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2, 155.9, 148.0, 143.0, 136.3, 134.2, 132.2, 128.6, 128.5, 126.9, 126.2, 120.8, 117.3, 116.3, 108.3, 107.4, 101.1, 65.2, 31.4. HRMS (CI) *m/z* calcd for $C_{29}H_{25}N_3O_2$ 447.1947, found 447.1949.

General Procedure for the synthesis of palladium complexes C1-C4: Under an argon atmosphere, $[Pd(CH_3CN)_2Cl_2]$ (75 mg, 0.3 mmol) was added to solution of **L** (0.3 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature for 2h, concentrated to dryness, washed with dry Et_2O and dried *in vacuo* to give the palladium dichloride complex. Yields and characterization data for compounds **C1-C4** are as follows:

Palladium complex C1. Following the general procedure, **C1** was obtained as a red solid (112 mg, 74%). X-ray quality crystals were grown by slow diffusion of AcOEt into a solution of **C1** in CH_2Cl_2. M.P. = 160-162 °C (dec.). $[\alpha]^{20}_D$= 235.4° (c 0.57, $CHCl_3$). ^1H NMR (500 MHz, C_2D_6CO): δ 8.89 (d, 1H, *J* = 5.4 Hz), 7.95 (t, 1H, *J* = 7.4 Hz), 7.73-7.18 (m, 10H), 6.91-6.74 (m 2H), 5.48-5.33 (m, 1H), 2.78-2.53 (m, 2H), 2.11-1.90 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.9, 150.65, 147.8, 143.9, 141.3, 139.5, 130.0, 129.4, 129.0, 128.9, 128.4, 127.6, 125.1, 125.0, 69.1, 66.0, 35.0, 32.6. HRMS *m/z* calcd for $C_{22}H_{20}N_3Pd$ 432.0674. Found 432.0678.

Palladium complex C2. Following the general procedure, **C2** was obtained as an orange solid (151 mg, 94%). X-ray quality crystals were grown by slow diffusion of *n*-hexane into a solution of **C2** in CH_2Cl_2. M.P. = 234-235 °C (dec.). $[\alpha]^{20}_D$= 177.5° (*c* 0.60, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.42 (d, 1H, *J* = 6.8 Hz), 7.58-7.17 (m, 11H), 6.93-6.81 (m, 2H), 6.64 (d, 1H, *J* = 2.5 Hz), 6.53 (dd, 1H, *J* = 6.8, 2.5 Hz), 5.06-4.86 (m, 1H), 3.83 (s, 3H), 2.78-2.54 (m, 2H), 2.17-1.92 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 167.8, 156.7, 151.2, 144.4, 142.3, 137.5, 129.6, 128.8, 128.5, 128.0, 127.8, 126.3, 110.0, 108.6, 68.4, 65.5, 56.5, 34.1, 31.2. HRMS *m/z* calcd for $C_{23}H_{23}ON_3ClPd$ 498.0557. Found 498.0559**.**

Palladium complex C3. Following the general procedure, **C3** was obtained as an orange solid (194 mg, 91%). X-ray quality crystals were grown by slow diffusion of *n*-hexane into a solution of **C3** in CH_2Cl_2. M.P. = 143-145 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.91 (bs, 1H), 7.85-7.74 (m, 3H), 7.64-7.35 (m, 11H), 7.58-7.17 (m, 11H), 7.29-6.92 (m, 1H), 7.11 (d, 1H, *J* = 7.9 Hz), 6.91 (s, 1H), 6.65-6.50 (m, 1H), 5.04-4.80 (m, 1H), 2.80-2.53 (m, 2H), 2.25-1.96 (m, 2H). ^{13}C NMR (175 MHz, $CDCl_3$): 160.0, 157.5, 142.4, 140.1, 139.9, 139.6, 137.1, 131.3 (q, $J_{C\text{-}F}$ = 34.4 Hz), 129.9, 129.0, 128.8, 128.3, 128.2, 126.1, 124.7, 123.1 (q, $J_{C\text{-}F}$ = 272.3 Hz), 123.4, 123.3, 121.9, 69.6, 66.7, 35.1, 33.1. HRMS (CI) *m/z* calcd for $C_{30}H_{23}N_3F_6Pd$ (M^+ - 2Cl) 645.0831, found 645.0841.

Palladium complex C4. Following the general procedure, **C4** was obtained as an orange solid (167 mg, 92%). X-ray quality crystals were grown by slow diffusion of *n*-hexane into a solution of **C4** in CH_2Cl_2. M.P. = 232-234 °C (dec.). $[\alpha]^{20}_D$= 472.6° (*c* 0.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.92 (d, 1H, *J* = 5.5 Hz), 7.75 (t, 1H, *J* = 7.8 Hz), 7.65-7.54 (m, 4H), 7.44-7.32 (m, 5H), 7.30-7.15 (m, 4H), 7.06 (s, 1H), 6.53 (m, 1H), 2.62-2.27 (m, 2H), 2.16-1.95 (m, 2H), 1.95-1.74 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 154.7, 152.8, 150.6, 140.2, 139.7, 129.1, 128.5, 127.8, 127.7, 124.7, 124.5, 63.9, 18.2. HRMS *m/z* calcd for $C_{23}H_{23}N_3Cl_2NaPd$ 504.0196. Found 540.0180 [M^++Na].

General procedure for the asymmetric Suzuki coupling:
A Schlenk flask containing a magnetic stir bar was charged with $Pd(OAc)_2$ (2.4 mg, 0.01 mmol), **L1** (4 mg, 0.015 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), boronic acid (0.3 mmol), and aryl bromide (0.2 mmol) under argon atmosphere. Mixture Toluene:H_20 9:1 (1

mL) was added, and the reaction was stirred at 80 °C during the indicated time for each case. The reaction mixture was filtered through a short pad of Celite and the Celite pad was washed with DCM. The combined organic layers were concentrated and the resulting residue was purified by flash chromatography using hexane–EtOAc mixtures as eluents.

(*S*)-2-methoxy-1,1'-binaphthyl (*S*)-5a (Table 3, entry 10). Following the general procedure after 15 hours. Flash chromatography (*n*-hexane→*n*-hexane:EtOAc 200:1) afforded **5a** (55 mg, 97%) as a white solid. $[\alpha]^{20}_{D}$ +8.0 (*c* 1.0, $CHCl_3$) for 88% ee. [Lit.[21]: $[\alpha]^{25}_{D}$= –31.4 (*c* 2.1, THF) for the (*R*)-enantiomer (99 % ee)]. Spectroscopic and physical data matched those reported in the literature.[9] HPLC (Chiracel OJ-H, 2-propanol/*n*-hexane 20:80, flow 1.0 mL/min, T = 30 °C): t_R 7.7 min (major) and 12.1 min (minor).

(*R*)-2-methoxy-1,1'-binaphthyl (*R*)-5a (Table 3, entry 12). $[\alpha]^{20}_{D}$ –7.9 (*c* 1.0, $CHCl_3$) for 82% ee. [Lit.[21]: $[\alpha]^{25}_{D}$= –31.4 (*c* 2.1, THF) for the (*R*)-enantiomer (99 % ee)]. Spectroscopic and physical data matched those reported in the literature.[9] HPLC (Chiracel OJ-H, 2-propanol/*n*-hexane 20:80, flow 1.0 mL/min, T = 30 °C): t_R 7.7 min (minor) and 12.1 min (mayor).

(*S*)-2,3-dimethoxy-1,1'-binaphthyl (5b) (Table 3, entry 13). Following the general procedure after 48 hours. Flash chromatography (*n*-hexane→*n*-hexane:EtOAc 200:1) afforded **5b** (56 mg, 89%) as a white solid. $[\alpha]^{20}_{D}$ +7.3 (*c* 0.58, $CHCl_3$) for 87% ee. [Lit.[9]: $[\alpha]^{25}_{D}$= 7.3 (*c* 0.33, $CHCl_3$) for the (*S*)-enantiomer (92% ee)]. Spectroscopic and physical data matched those reported in the literature.[9] HPLC (Chiracel OJ-H, 2-propanol/*n*-hexane 30:70, flow 1.0 mL/min, T = 30 °C): t_R 6.1 min (major) and 9.2 min (minor).

(*S*)-2-Methoxy-1-(2-methylphenyl)-naphthalene (5c) (Table 3, entry 14). Following the general procedure after 96 hours. Flash chromatography (*n*-hexane→*n*-hexane:EtOAc 200:1) afforded **5c** (49 mg, 98%) as a white solid. $[\alpha]^{20}_{D}$ +24.7 (*c* 1.0, $CHCl_3$) for 67 % ee. [Lit.[22]: $[\alpha]^{25}_{D}$= +19.4 (*c* 1.0, DCM) for the (*S*)-enantiomer (46% ee)]. Spectroscopic and physical data matched those reported in the literature.[23] HPLC (Chiracel OJ-H, 2-propanol/*n*-hexane 10:90, flow 1.0 mL/min, T = 30 °C): t_R 5.4 min (major) and 6.6 min (minor).

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5. References and notes

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