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Tunable P-Stereogenic P,N-Phosphine Ligands Design: Synthesis and Coordination Chemistry to Palladium

Sébastien Lemouzy, Marion Jean, Fabien Deplante, Muriel Albalat, Damien Héroult,* and Gérard Buono*^[a]

The synthesis of P,N heterobidentate phosphine / palladium complexes has been realized from P-stereogenic enantiopure ligands. Five, six or seven membered ring complexes have been fully characterized, notably by X-ray diffraction, allowing

the study of the chelation to a "palladium (II) dichloride" unit. The nature of nitrogen coordination site as well as the size of the ring modify the bite-angle at the solid state.

Introduction

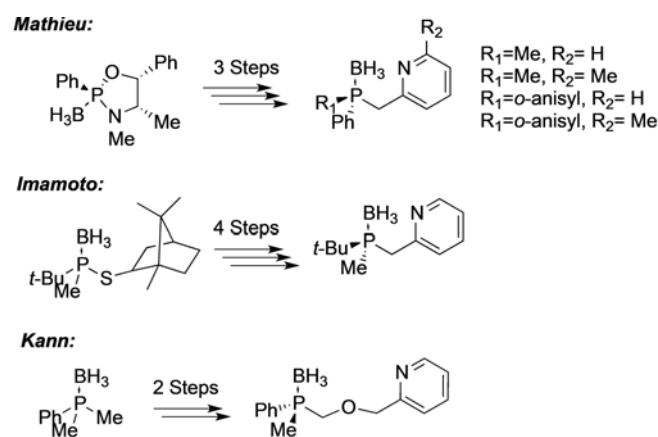
Heterobidentate P,N-ligands are interesting ligands as these compounds may bound to a metal centre both by a "soft" (phosphorus atom) and a "hard" (nitrogen atom) coordination site.^[1] The ability of bis-ligands possessing both hard and soft characters through heteroatoms enables a fine tuning in stabilization of various intermediates in catalytic cycles. Thus P,N-ligands have shown a high efficiency in a wide array of catalytic processes. In particular, P,N-ligands possessing a sp² hybridized nitrogen donor (such as a pyridine or an oxazoline ring) present unique coordination properties, owing to the electron disparity between the two distinct coordination sites.^[2]

This electron disparity has been exploited in the palladium-catalyzed enantioselective allylic substitution^[1b,3] or α -arylation of carbonyls.^[2d,4] Recently, PHOX-type ligands, complexed to nickel, have also performed very well in asymmetric arylation of cyclic aldimines.^[5] In earlier studies, Imamoto and coll.^[6] have synthesized P-stereogenic phosphine/oxazoline ligands and applied to Pd-catalyzed allylic substitution of 1,3-diphenyl-1-acetoxy-2-propene with dimethyl malonate. These ligands are very efficient and, interestingly, a remarkable switch in enantioselectivity was observed when the Pd/ligand ratio was changed revealing the hemilabile behaviour of these P,N-ligands in their palladium complexes.

During the last three decades, the important developments of the Suzuki-Miyaura cross-coupling have been mostly achieved through ligand design,^[7] notably the reaction of sterically-hindered coupling partners to form enantioenriched axially chiral biaryl compounds, which still remains a major challenging area.^[8-11] The α -arylation of carbonyl compounds catalyzed by palladium or nickel has also been the subject of

numerous studies, starting from the seminal work reported simultaneously by Buchwald^[12] and Hartwig.^[13] In this context, the KenPhos ligand was also used to promote the formation of chiral quaternary carbon atom in very high yields and enantioselectivities.^[14] The stereogenic character of the phosphorus atom was highlighted by a strong match-mismatch effect, which showed the importance of the vicinity between the chiral centre and the metal. In 2012, the group of Mazet used P-stereogenic phosphine-pyridine ligands with a binepine backbone to realize the α -arylation of aldehyde with good to excellent yields and enantioselectivities.^[15]

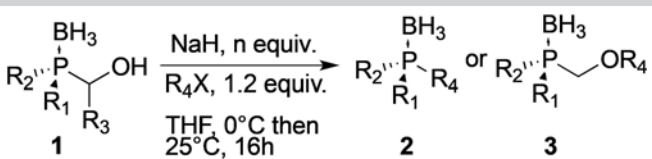
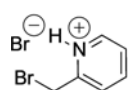
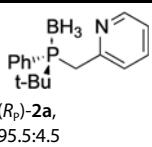

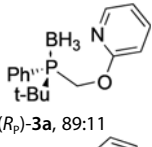
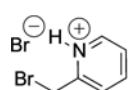
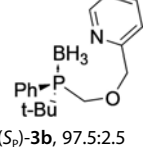
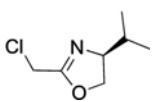
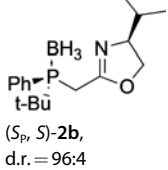
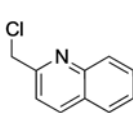
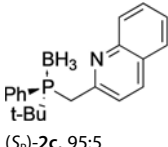
For the design of chiral P,N-phosphine ligands able to complex transition metal, the introduction of the chiral information directly on the phosphorus atom has been initiated by Mathieu,^[16] Imamoto^[17] or Kann^[18] (Scheme 1). Their synthe-



Scheme 1. Synthesis of P,N preligands developed by Mathieu,^[16] Imamoto^[17] and Kann.^[18]

ses are based on the reactivity of oxazaphospholidine-boranes developed by Jugé,^[19] as well as those of chiral phosphine-boranes at low temperature or the desymmetrization of dimethylphosphine-borane. In this report, we synthesize new heterobidentate ligands under mild conditions based on our

Table 1. Synthesis of P-stereogenic P,N-ligands 2-3

Entry	1	n	R ₄ X	Yield (%)	2 or 3 e.r. after reaction
					
1	(<i>R_p</i>)- 1a , e.r. = 95:5 d.r. ≈ 1:1 R ₁ = <i>t</i> -Bu, R ₂ = Ph, R ₃ = Me	3		79	 (<i>R_p</i>)- 2a , 95.5:4.5
2	(<i>R_p</i>)- 1b , e.r. = 98:2 R ₁ = <i>t</i> -Bu, R ₂ = Ph, R ₃ = H	1.2		47	 (<i>R_p</i>)- 3a , 89:11
3	(<i>S_p</i>)- 1b , e.r. = 98:2 R ₁ = Ph, R ₂ = <i>t</i> -Bu, R ₃ = H	2.5		80	 (<i>S_p</i>)- 3b , 97.5:2.5
4	(<i>S_p</i>)- 1a , e.r. = 95:5, d.r. ≈ 1:1 R ₁ = Ph, R ₂ = <i>t</i> -Bu, R ₃ = Me	1.5		74	 (<i>S_p</i> , <i>S</i>)- 2b , d.r. = 96:4
5		1.5		87	 (<i>S_p</i>)- 2c , 95:5

previous studies relying the peculiar reactivity of P-stereogenic hydroxyalkylphosphine-boranes.^[20] Recently, this methodology was used with success by Mezzeti and coll. to prepare enantiopure C₂-P(NH)-P ligand.^[21]

Results and Discussion

Synthesis of the P-stereogenic P,N-ligands

In view of the importance of P,N-ligands, we have decided to synthesize a family of palladium complexes possessing a P-stereogenic P,N-ligand, starting from our previously synthesized P-chiral compounds (Table 1, Entries 1 and 3-5).^[20]

For the synthesis of the ligand **3a** (Entry 2), we have developed an O-alkylation method of substrate **1b** via a nucleophilic aromatic substitution. For this S_NAr reaction, the exclusive formation of the desired O-arylated product **3a** was observed. However, despite a very good reactivity at 25°C (86 % yield in THF), a significant erosion of the chiral information of (*R_p*-**3a**) was observed (e.r. = 77:23). Changing the solvent to DMF led to lower yield (40%) and almost complete racemization. We postulated that the racemization could be due to the

generation of the sodium phosphido-borane by retroaddition. Indeed, inversely to the hard alcoxide, the soft phosphido-borane is not prone to react with the *o*-fluoropyridine according to S_NAr reaction. When the reaction temperature is lowered to 0°C, the transformation occurs with still partial racemization on the phosphorus atom (e.r. = 89:11), although the rate of the formation of **3a** is largely dropped down (47 % yield). To improve this method, we examined other leaving group (Cl, Br, OTf). However, this study showed that fluoride is by far the best leaving group, producing **3a** with the best yields and enantiomeric ratio. The latter can be optimum (e.r. = 98:2) when the reaction temperature is lowered to -20°C at the expense of the yield (22%).

Synthesis of the dichloro(P*,N)-palladium (II) complexes

The optimization of the synthesis of the palladium complex from *rac*-**2a** was realized according to the work of Mazet and coll..^[15] (Table 2). First, the deprotection of **2a** with diethylamine for 60h generated the free phosphine. Then, after removal of the formed amine-borane complex in vacuo, it was treated with dichlorobis(acetonitrile)palladium (II) at room temperature

Table 2. Optimization of the deprotection conditions of the phosphine-borane **2a** for the synthesis of complex **[PdCl₂-2a]**

Entry	T °C	t (h)	yield ^[a] (%)
1	80	60	73
2	80	24	73
3	80	6	46
4	40	60	69
5	40	15	37

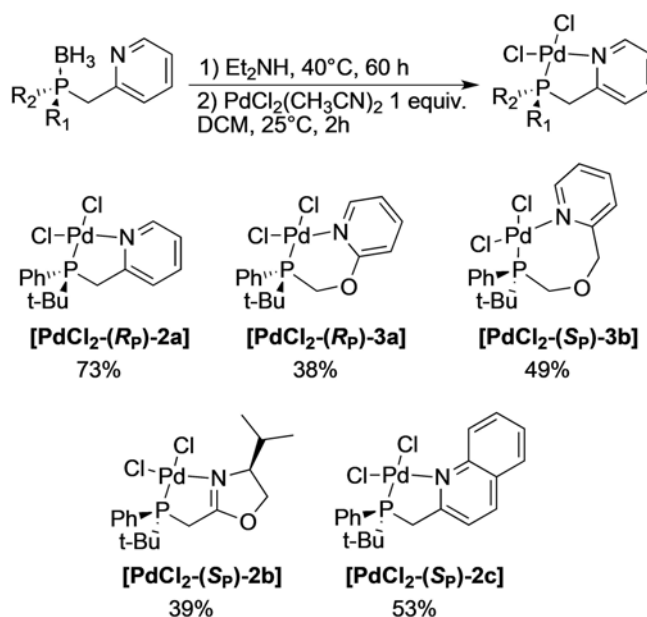
[a] isolated yield after column chromatography

in dichloromethane to afford the desired complex **[PdCl₂-2a]**. Its remarkable stability allowed its purification by column chromatography on silica gel (73 % yield) (Table 2, Entry 1).

The formation of the palladium complex **[PdCl₂-2a]** was monitored by ³¹P NMR through the significant deshielding of P signal with respect to **2a** (the complex shows a singlet at δ = 60.4 ppm and the phosphine-borane **2a** shows a “quartet” at δ = 32.9 ppm). In addition, the *ortho*-hydrogen of the pyridine ring also undergoes a significant deshielding in ¹H NMR upon complexation (δ = 9.67 ppm for the complex and δ = 8.37 ppm for **2a**), confirming the complexation of the nitrogen atom on the palladium centre. The deprotection step was deeper examined and noted that the yield of the palladium complex is not affected by decreasing the reaction time to 24 hours (Entry 2) but an important decrease was observed if the reaction time was decreased to 6 hours (Entry 3, 46 % yield). Finally, the temperature variations showed that the deprotection reaction proceeded equally at 40 °C in 60 hours (Entry 4, 69 % yield). However, at that temperature, the reaction time could not be shortened, otherwise the conversion dropped down (Entry 5, 37 % yield). The conditions of Entry 4 were selected as the optimal conditions to avoid the possible partial racemisation of the enantioenriched P-stereogenic substrates at 80 °C. In these conditions, a family of enantiopure palladium complexes based on P-stereogenic P,N-ligands has been synthesized (Scheme 2). To guarantee an optimum optical purity, the preligands **2-3** can be purified by preparative chiral HPLC before their use (See SI, Table 1).

Coordination chemistry of the dichloro(P*,N)-palladium (II) complexes

In order to gain information on the coordination properties of these complexes, we tried to gather crystallographic data on the solid state. By crystallizing the pure complexes in DCM / heptane, suitable crystals have been obtained to allow X-ray diffraction analysis (Figure 1). The spectral data of the different complexes were gathered and are summarized in Table 3. The main particularity of these complexes is that there seems to be a correlation between the size of the chelate and the chemical



Scheme 2. Synthesis of a family of palladium (II) chloride complexes bearing a P-stereogenic P,N-ligand.

shift in ³¹P and ¹H NMR. We observed a shielding of the chemical shift of the phosphorus atom with the size of chelate (complexes **PdCl₂-2a**, **PdCl₂-3a** and **PdCl₂-3b** which form five, six and seven-membered chelates feature chemical shifts of 60.4, 33.1 and 17.1 ppm in ³¹P NMR, respectively). The same trend is observed when considering the chemical shift of the *ortho* hydrogen *H_A* of the pyridine ring (the complexes **PdCl₂-2a**, **PdCl₂-3a** and **PdCl₂-3b** exhibit a chemical shift of 9.67, 9.41 and 8.89 ppm respectively).

When looking at the difference of chemical shift (Δδ) between the complex and the starting phosphine-borane, the same conclusions apply in ³¹P NMR. Nevertheless, the difference between the five and six-membered chelate becomes less significant by ¹H NMR, as the two corresponding complexes **[PdCl₂-2a]** and **[PdCl₂-3a]** show a deshielding of about 1.25 ppm for the *ortho* proton *H_A* of the pyridine ring. Even though these palladium complexes display numerous similarities, especially when looking at the Pd-Cl bond lengths, some differences may arise from their structures. Indeed, the complex **[PdCl₂-3a]** features a shorter Pd-N bond and a longer Pd-P than those of the complex **[PdCl₂-2a]**, which may be rationalized by the increased σ-donor ability of the ligand which possesses an oxygen atom *ortho* to the nitrogen in the pyridine ring (**3a**). The dissymmetry between the Pd-N and Pd-P bonds is even more significant for the complex **[PdCl₂-2b]** compared to the complex **[PdCl₂-2a]** having the same chelate ring size. The presence of the oxazolidine ring decreases the Pd-N bond but increases the Pd-P bond. Likewise, **[PdCl₂-2c]** possess the longest Pd-N bond among the complexes we have synthesized, which may account for the reduced electron density of the quinoline nitrogen, when compared with a pyridine ring.^[22] Moreover, even though the palladium displays a square planar

coordination geometry in these complexes, the complexes [PdCl₂-2a], [PdCl₂-3a] and [PdCl₂-2b] feature an almost perfect square planar geometry ($\phi_1 < 2^\circ$), while a slight distortion (ϕ_1

$\approx 4^\circ$) is observed for complex [PdCl₂-3b]. A higher distortion ($\phi_1 \approx 10^\circ$) is observed for complex [PdCl₂-2c], which could be attributed to the steric repulsion between the quinoline group

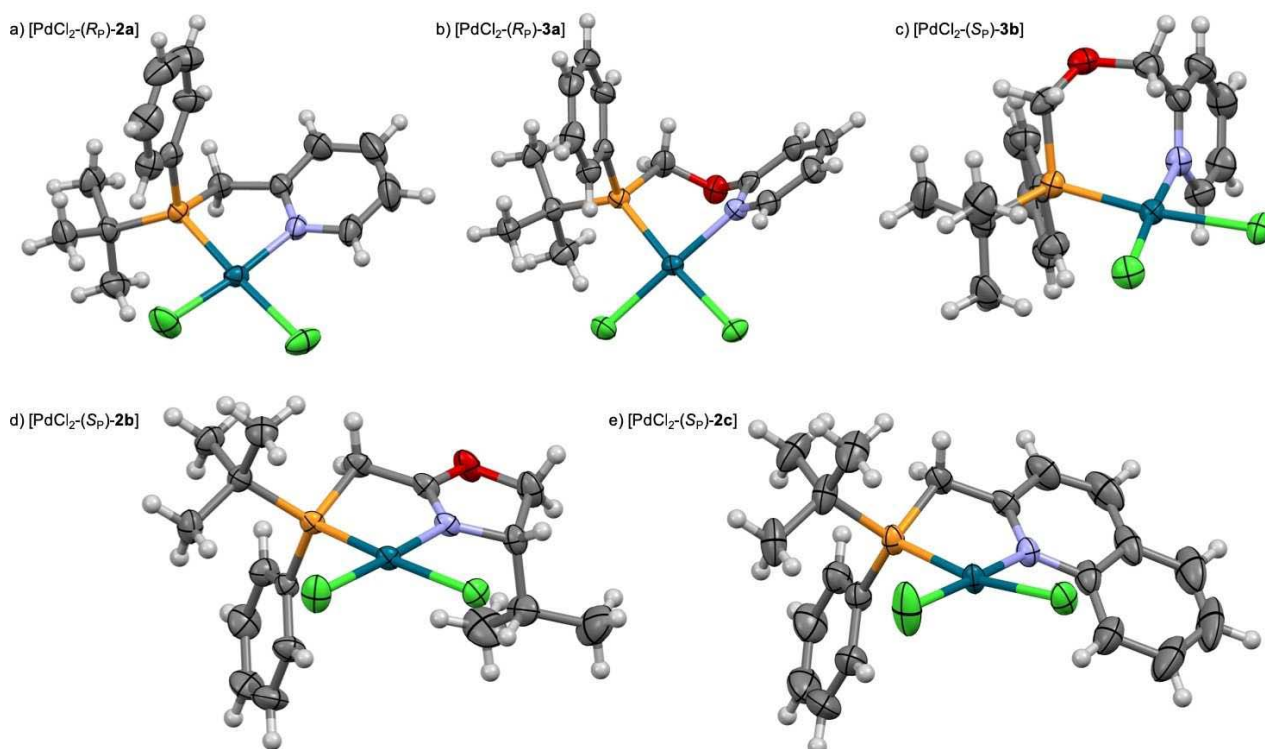


Figure 1. X-ray structure of enantiopure complexes. Thermal ellipsoids are set at 50% probability.

Table 3. Spectral and crystallographic data of the synthesized enantiopure palladium (II) complexes 2-3

Complex	[PdCl ₂ -2a]	[PdCl ₂ -3a]	[PdCl ₂ -3b] ^[c]	[PdCl ₂ -2b]	[PdCl ₂ -2c]
δ (³¹ P NMR) ^[a]	60.4	33.1	17.1, 19.6	44.4	70.3
$\Delta\delta$ (³¹ P NMR) ^[b]	+27.5	+3.3	-12.5, -10	+12.3	+37.9
δ (H _N , ¹ H NMR) ^[a]	9.67	9.41	8.89, 9.32	n.a.	n.a.
$\Delta\delta$ (H _N , ¹ H NMR) ^[b]	+1.33	+1.22	+0.31, +0.74	n.a.	n.a.
Pd-N (Å)	2.067(3)	2.052(2)	2.051(4)	2.035(3)	2.092(4)
Pd-P (Å)	2.2145(9)	2.2515(8)	2.2673(16)	2.2303(9)	2.2179(13)
Pd-Cl ₁ (Å)	2.3836(10)	2.3581(7)	2.3716(16)	2.3637(9)	2.3861(13)
Pd-Cl ₂ (Å)	2.2908(11)	2.2760(8)	2.2673(16)	2.2934(9)	2.2764(15)
Cl ₁ -Pd-Cl ₂ (°)	90.63(4)	90.39(3)	90.57(6)	90.84(3)	88.94(6)
Cl ₁ -Pd-P (°)	176.72(4)	175.24(3)	172.63(5)	174.49(3)	168.36(6)
Cl ₁ -Pd-N (°)	93.78(8)	88.05(7)	86.10(13)	92.56(8)	96.08(13)
Cl ₂ -Pd-P (°)	92.38(4)	94.37(3)	95.97(6)	94.66(3)	93.09(6)
Cl ₂ -Pd-N (°)	174.52(9)	177.77(7)	176.18(14)	176.60(8)	174.80(13)
β_n = P-Pd-N (°)	83.14(8)	87.20(7)	87.47(13)	81.93(8)	82.27(13)
ϕ_1 = dihedral angle (°) ^[d]	1.93	1.27	4.09	0.36	9.98
ϕ_2 = dihedral angle (°) ^[e]	10.41	68.47	72.67	15.69	27.87
%V bur ^[f]	43.6	46.3	47.4	46.2	46.5

[a] NMR recorded in CDCl₃, values in ppm. [b] $\Delta\delta = \delta$ (complex) - δ (phosphine-borane). [c] this complex features a 2:1 mixture of conformers, the first number refers to the major conformer, and the second one refers to the minor conformer. [d] The dihedral angle ϕ_1 is measured between N-Pd-P and Cl₁-Pd-Cl₂ planes. [e] The dihedral angle ϕ_2 is measured between N-Pd-P and C-N-C planes. [f] %V bur was calculated according to ref.^[23]

and the chlorine atom ($d_{\text{H10-Cl1}} = 2.6 \text{ \AA}$). It is noteworthy that for all the complexes the phenyl and *tert*-butyl group bound to the phosphorus atom occupy pseudo-axial and equatorial position respectively. Finally, the bite angle of these P,N-ligands in these complexes are also different, the seven-membered ring one [PdCl₂-**3b**] having a slightly higher bite angle ($\beta_n = 87.47^\circ$) than the six-membered one [PdCl₂-**3a**] ($\beta_n = 87.20^\circ$) but much higher than the five-membered ones ($\beta_n = 83.14^\circ$, 82.27° and 81.93° for [PdCl₂-**2a**], [PdCl₂-**2c**], [PdCl₂-**2b**] respectively). In the case of the six-membered chelate complex, due to its boat conformation, the pyridine ring is forced to lay away from the palladium coordination plane ($\phi_2 = 68.5^\circ$). The same observation can be made for the seven-membered ring chelate complex where the pyridine ring is almost orthogonal to palladium coordination plane ($\phi_2 = 72.7^\circ$). These angles are higher than the ones in the complexes [PdCl₂-**2a**], [PdCl₂-**2b**] and [PdCl₂-**2c**] (10.4° , 15.7° and 27.9° respectively). Considering the pyridine complexes [PdCl₂-**2a**, -**3a** and -**3b**], we observed the same variation of the bite angle with the %Vbur^[23] as well as the distortion angle ϕ_2 . As expected for the complexes [PdCl₂-**2a**, **b** and **c**], we observed that the %Vbur is related to the steric hindrance around the nitrogen coordination site.^[24] It is also noteworthy that for the complex [PdCl₂-**3b**], the two phenyl groups are quasi-parallel and distanced by only 3-5 Å at the solid state. We have also observed, on the self-assembly pattern of complexes, intermolecular C-H hydrogen bonding interactions (from 2.7 to 3.3 Å) as reported by Pons and coll. on the N-pyrazole, P-phosphine complexes.^[25]

Having in hands these new P-stereogenic heterobidentate ligands/palladium complexes, they were tested in two C-C cross coupling reactions. In the Suzuki-Miyaura coupling reaction and the intramolecular α -arylation of ketones **4**, the best results, 92% and 65% yield respectively, were obtained with the 7-membered ring ligand (*S_p*)-**3b** (Scheme 3, see Supporting

Information for the experimental procedures and the complete study (Table 4 and 6) and evaluation of ligand, base, solvent, nature of aryl halide, palladium source).

Conclusions

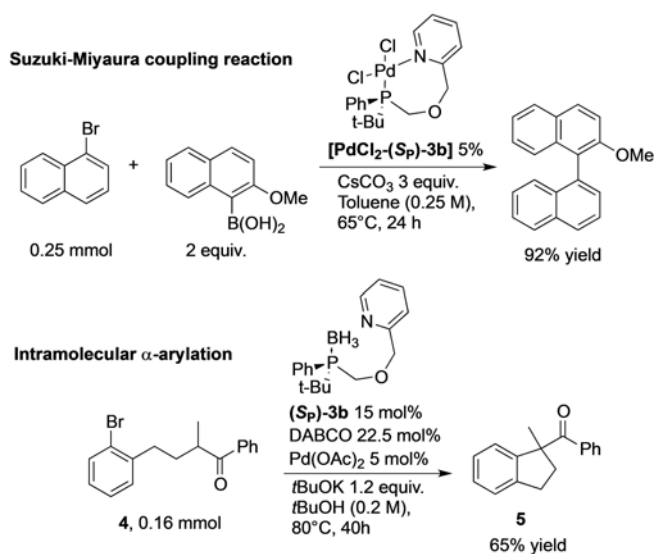
In conclusion, we have synthesized a family of palladium complexes bearing P-stereogenic P,N-heterobidentate ligands by our synthetic approach. The structures of these new complexes have been fully characterized by spectroscopic and crystallographic studies. The effect of the chelate size and the effect of the nature of the nitrogen coordination site were evidenced. These ligands are potential good candidates for further catalyst optimization and design. Our future investigations include coordination of such ligands to other transition metals and the development of performant catalytic methods using isolated transition-metal complexes bearing these ligands.

Supporting Information Summary

Experimental procedures for the preparation of enantiopure preligands **2-3** and their palladium complexes have been included. Products characterization and NMR spectra of all new compounds as well as complete crystallographic description of the complexes are described. In addition of the Scheme 3, the optimization of the reaction conditions is indicated as well as the screening of the preligands **2-3**.

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Scheme 3. Best results obtained with the 7-membered ring ligand (*S_p*)-**3b** in the Suzuki-Miyaura coupling reaction and the intramolecular α -arylation of ketone **4**

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