Pd(II) complexes of monodentate deoxycholic acid derived binaphthyl diamido phosphites as chiral catalysts in the asymmetric Suzuki-Miyaura cross-coupling

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ABSTRACT

Chiral binaphthyl diamidophosphites derived from deoxycholic acid were synthesized and used as ligands for the preparation of mononuclear Pd(II) complexes, which were employed as catalysts in the asymmetric Suzuki–Miyaura cross-coupling of arylboronic acids with aryl bromides. Amongst the different reaction parameters, the substrate concentration emerged as being crucial for the outcome of the reaction: the reaction was faster in a concentrate reaction mixture, allowing to work at 0 °C, where the reaction promoted by the Pd-complexes resulted more enantioselective affording cross-coupling products with ee up to 70% .

INTRODUCTION

Asymmetric catalysis with transition metal complexes represents a powerful method to obtain valuable enantiomerically enriched products having different structures:[1] as a matter of fact enantioselective oxidation,[2] hydrogenation[3] and C-C bond forming reactions[4] can be effectively performed under asymmetric metal catalysis conditions. In this research area, the enantiomerically pure ligand and its metal complexes play the main role for the chemical as well as stereochemical outcome of the reaction. For this reason, a great deal of synthetic efforts is addressed to the design and achievement of enantiopure ligands and metal complexes leading to efficient and selective organic transformations. In this field enantiopure phosphorus ligands are successfully used in different metal catalyzed asymmetric reactions and, among them, monodentate phosphorus ligands with P-heteroatom bonds, such as phosphites,[5] phopsphoramidites,[6] phosphinites and phosphonites[7]

represent good alternatives to the bidentate chiral phosphane ligands. This kind of ligands can be obtained more easily than the bidentate ones, they are more stable than phosphanes and a great variety of structures are accessible, starting from amines or alcohols having different structural and stereochemical features. In addition, the convenient choice of the atoms bonded to phosphorus (only oxygen, nitrogen and oxygen, carbon and oxygen) allows fine-tuning of the donor-acceptor characteristics of the phosphorus atom, which affect the coordination properties of the ligand.

In the last ten years enantiopure diamidophosphites, which present two P-N bonds embedded in a phospholidine ring and an exocyclic P-O bond, have emerged as promising phosphorus ligands. The possibility to change both nitrogen and oxygen substituents allows a high control on the steric and electronic characteristics of these ligands. In addition, the presence of two substituted nitrogen atoms increases the steric hindrance and the electronic density of the phosphorus atom with respect to phosphites and phosphoramidites. Chiral diamidophosphites, both mono- and bidentate, have been used in different enantioselective C-C bond forming reactions, such as Pd-catalyzed allylic substitutions,[8] Pd-catalyzed cycloaddition,[9] Pd-catalyzed hydrovinylation,[10] Rh-catalyzed hydroformylation,[11] Cu and Rh-catalyzed conjugate addition of organometallic reagents to enones.[12] However, despite the success obtained in different Pd-catalyzed enantioselective reactions, to the best of our knowledge no examples concerning the use of diamidophosphite ligands in the Pd-catalyzed asymmetric Suzuki-Miyaura cross-coupling reaction are reported in the literature, although this reaction has received a great deal of attention because of the interest in the biaryl reaction products, whose structural motif is present in chiral auxiliaries[1c] as well as in bioactive compounds.[13] Other kind of chiral phosphorus ligands have been used to this aim, mainly bidentate ligands, such as bishydrazones[14] or phosphine-carbene ligands,[15] and bulky monophosphines.[16] Some years ago we demonstrated for the first time that chiral monophosphites can be used as enantioselective Pd-ligand in the asymmetric Suzuki-Miyaura cross-coupling reaction.[17] These ligands were biaryl phosphites of deoxycholic acid and the success in the Suzuki-Miyaura reactions was allied to the bulkiness of the phosphites, which allow to form in the reaction environment a monosubstituted catalytic Pd-complex, believed crucial for the outcome of the reaction. Following our interest in deoxycholic acid derived chiral ligands to be used in asymmetric catalysis[18] we envisaged that monodentate diamidophosphites having a binaphthyl diazaphospholidine moiety linked to the steroidal scaffold of deoxycholic acid could be interesting ligands for Pd-catalyzed asymmetric Suzuki-Miyaura cross-coupling reaction, aimed at obtaining optically active biaryl derivatives. In this paper we describe the synthesis and characterization of the ligands **1a-b** and their disubstituted mononuclear Pd(II)-complexes ($PdCl_2L_2$) **2a-b** (Figure 1), as well as the use of

these Pd-complexes as catalytic precursors for the asymmetric Suzuki-Miyaura cross-coupling reaction.

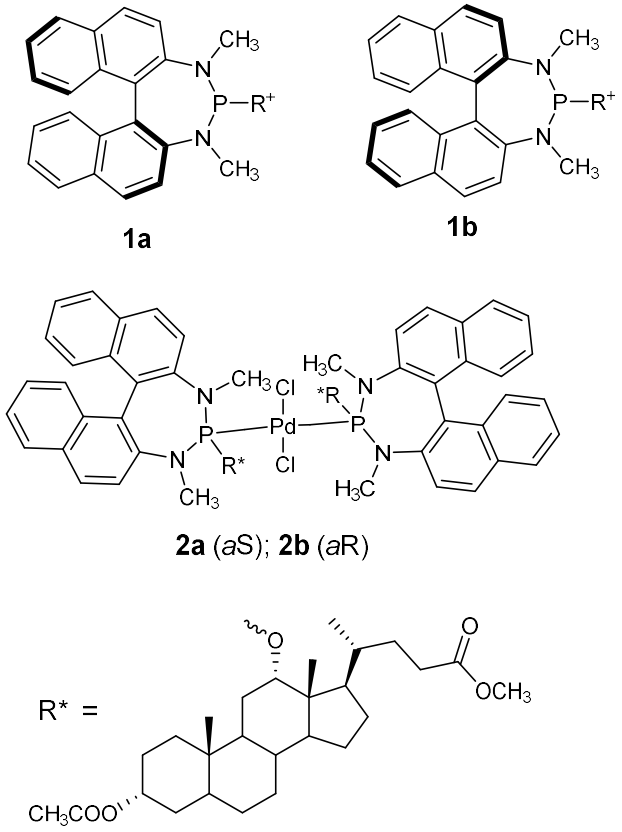
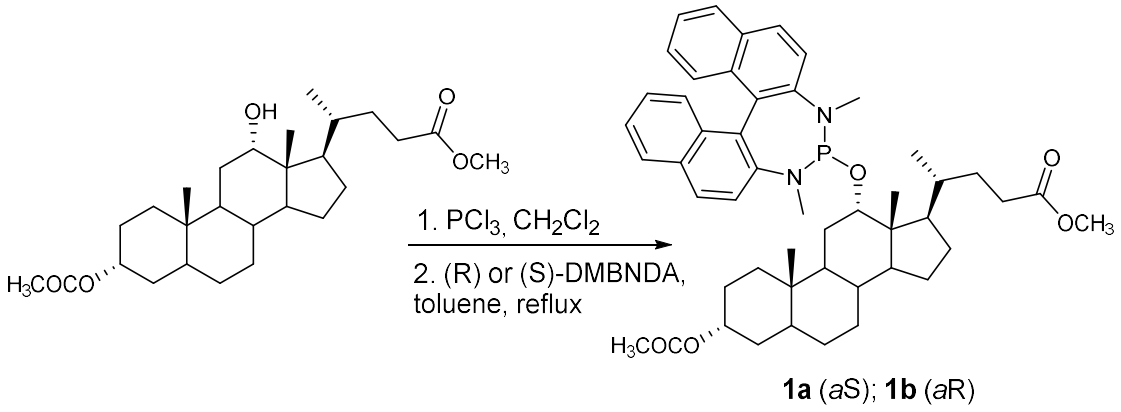


Figure 1: Structure of ligands and Pd(II) complexes

RESULTS AND DISCUSSION

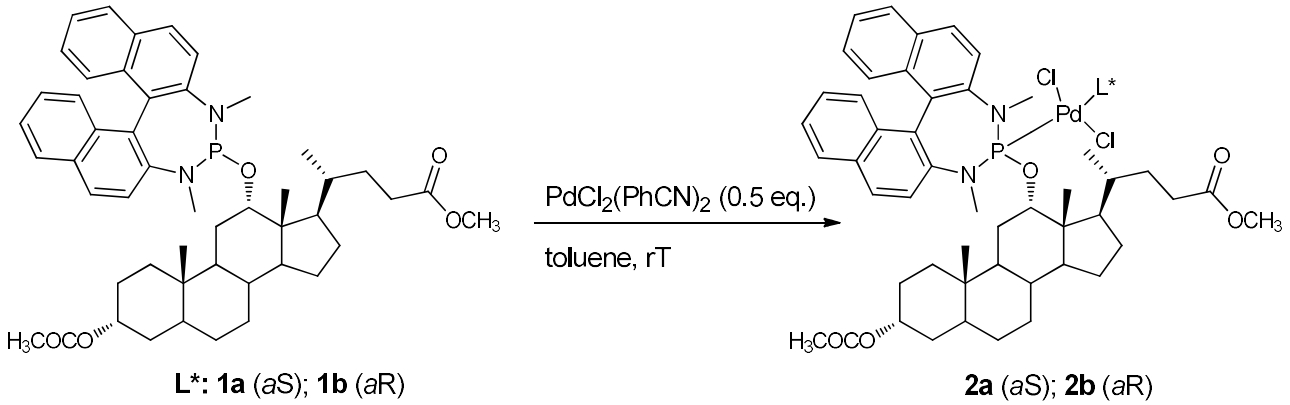
Synthesis and characterization of ligands and complexes

The diamido phosphites **1a-b** were synthesized in two consecutive steps, by reacting methyl 3-acetyloxy-12-hydroxydeoxycholan-24-ate with PCl_3 in the presence of trimethylamine, and successive reaction of the crude bis-chlorophosphite with (R)- or (S)-N-N'-dimethyl-1,1'-binaphthalenediamine (DMBNDA) (Scheme 1) in boiling toluene, according to our previously described synthetic procedure.[18h]



Scheme 1: Synthesis of ligands **1a** and **1b**

The preparation and characterization of the new diamido phosphites **1a-b** are reported in the Experimental Section. The complexes **2a-b** of general formula $PdCl_2L_2$ were prepared by reacting two equivalents of ligand with $PdCl_2(PhCN)_2$ in toluene at room temperature (Scheme 2) for 15 min.



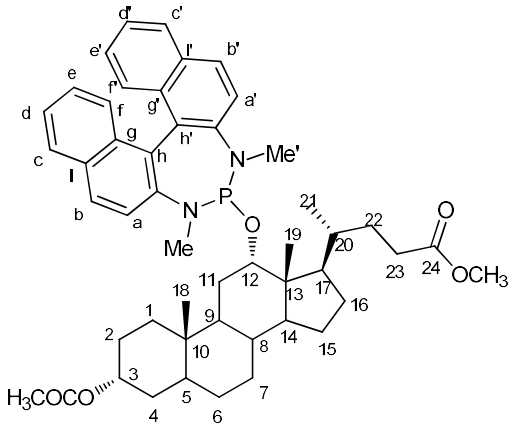
Scheme 2: Synthesis of Pd (II)-complexes **2a** and **2b**

The Pd(II) complexes were obtained as yellow solids in almost quantitative yield. They are stable at room temperature under inert atmosphere and soluble in common organic solvents. They were fully characterized in solution by multinuclear (^{1}H, ^{31}P and ^{13}C) NMR spectroscopy: bidimensional ^{1}H-^{13}C HMBC, ^{1}H-^{13}C-HSQC, ^{1}H-^{1}H NOESY and ^{1}H-^{1}H COSY experiments were necessary to assign the majority of the signals.

The coordination of the ligand to the Pd center shifts the ^{31}P signal at higher fields in both the complexes (117.1 ppm for **2a** and 115.8 ppm for **2b**) with respect to the ^{31}P signal in the corresponding ligands (168.8 ppm for **1a** and 159.4 ppm for **1b**), probably because of the low σ–donor character of the ligands, as observed for other kind of Pd(II) complexes with diamido phosphite ligands.[8e] Table 1 collects the signals of protons that are shifted because of the coordination of the ligand to the metal center: the different extent of the shift for corresponding

protons of the two diastereomeric complexes is reasonably the result of different arrangements of the ligands in the two complexes.

Table 1: Chemical shift (ppm) for relevant protons in ligands and complexes



Protons	δ_H **1a**	δ_H **2a**	δ_H **1b**	δ_H **2b**
a	7.50	8.44	7.66	8.15
b	7.72	8.04	7.95	8.28
a'	7.41	7.53	7.78	8.58
b'	7.76	7.64	7.80	8.07
1	1,90, 1.01	0.04, -0.20	1.72, 0.89	1.15, 1.68
2	1.70, 1.42(1)	0.98, 0.67(1)	1.89, 1.74	1.86, 2.11
3	4.72	4.56	4.91	4.94
4	1.85, 1.69(1)	1,61, 1.39(1)	1.77, 1.55	1.52, 1.67
5	1.17	0.88	1.22	1.13
8	1.38	1.45	2.16	1.30
11	1.69, 1.33	0.76, 0.70	2.13, 1.35	1.74, 3.51
12	4.28	4.78	4.35	6.16
14	1.72	1.64	1.67	1.43
17	1.94	3.01	1.95	2.08
18	0.82	0.47	0.82	0.54
21	0.98	1.57	1.00	1.64
NMe	2.92	3.99	2.83	3.58
NMe'	2.89	3.67	3.03	3.53

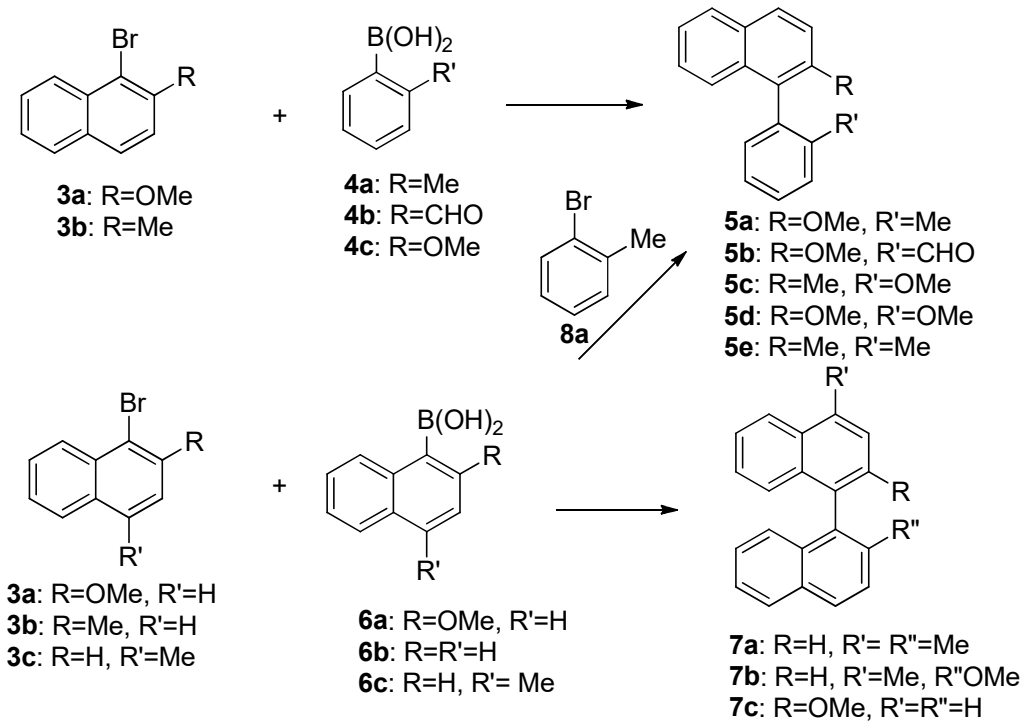
(1) These signals can be attributed both to protons 2 and 4

As far as the binaphthyl moiety is concerned, the coordination affects mainly the protons *a*, *b* and *a',b'* , which are closer to the P atom. The extent of the shift upon coordination is higher for *a* than for *b* in both the complexes, reasonably due to the higher distance of *b* from P, and hence from Pd. The coordination affects in different way the protons *a'* and *b'* of the two complexes: a low shift is observed for these protons when comparing **1a** and **2a**, whereas a shift comparable to that of protons *a* and *b* is detected when comparing **1b** and **2b**. Other significant differences are found for

protons of the cholestanic backbone, which can be the result of conformational differences between the two complexes. The higher shifts observed for protons 1 2 and 5 in passing from **1a** to **2a** can suggest a proximity of the Pd center to the A ring of the steroidal skeleton in **2a**, whereas the higher shifts of protons 12, 8 and 11 in going from **1b** to **2b** indicate that in complex **2b** Pd is closer to the C ring of the cholestanic moiety.

Asymmetric Suzuki-Miyaura cross-coupling

The reaction between 1-bromo-2-methoxynaphthalene **3a** with ortho-tolylboronic acid **4a** (Scheme 3) promoted by the chiral Pd(II) complexes **2a-b** was chosen as the model system for screening of the reaction conditions (Table 2).



Scheme 3: Asymmetric Suzuki-Miyaura biaryl coupling

Although most of the Suzuki-Miyaura cross-coupling reactions are carried out in organic solvent-water medium, both biphasic and homogeneous, dry solvents were used because of the water sensitivity of the Pd-complexes.

Table 2: Asymmetric Suzuki–Miyaura cross-coupling of **3a** and **4a**[1]

Run	Pd complex	Base	Solvent	Conc (M)	T (°C)	t (h)	Yield %[2]	e.e. %[3]	AC[4]
1	**2a**	Cs_2CO_3	Toluene	0.02	40	14	96	6	(-)
2	**2a**	Cs_2CO_3	Toluene	0.02	rT	48	96	7	(-)
3	**2b**	Cs_2CO_3	Toluene	0.02	40	14	96	22	(+)
4	**2b**	Cs_2CO_3	Toluene	0.02	rT	48	96	25	(+)
5	**2b**	CsF	Toluene	0.02	40	14	95	22	(+)
6	**2b**	CsF	Toluene	0.02	rT	48	94	27	(+)
7	**2b**	Cs_2CO_3	DME	0.02	rT	40	93	24	(+)
8	**2b**	Cs_2CO_3	THF	0.02	rT	40	94	22	(+)
9	**2b**	Cs_2CO_3	Toluene	0.1	rT	16	95	25	(+)
10	**2b**	Cs_2CO_3	Toluene	0.1	0	48	94	36	(+)

1.The reactions were stopped at complete conversion of the substrate or when it did not proceed further.
2. NMR yield
3. Enantiomeric excess (ee) determined by enantioselective HPLC (Chiralcel OJ, hexane/2-propanol 99/1, 1.0 mL/min, T=25°C, λ=230nm)
4.Sign of the specific rotation of the sample

Dry reaction conditions affect the solubility of the bases, therefore the use of bases having some solubility in organic solvents, such as CsF or Cs_2CO_3, is mandatory: nevertheless the reaction mixtures are always suspensions.

At first the reaction was performed in toluene at 40 °C with 5% catalyst loading, using the complex **2a**, two equivalents of Cs_2CO_3, with an aryl bromide concentration of 0.02 M (entry 1): the reaction was complete in 14 hours but the product was obtained only in 6% ee. Lowering of the temperature slowed down the reaction rate, but it did not improve the enantioselectivity (entry 2). The use of the distereomeric complex **2b** gave the same results in terms of yield and reaction rate, both at 40° C and at rT, but the enantioselectivity was much better: the cross-coupling product was obtained in 22% ee at 40° C (entry 3) and in 25% ee. at rT.

These results point out the matched relationship between the (R) absolute configuration of the biaryldiamido phosphite moiety and the stereochemistry of cholestanic backbone. In addition, unlike observed with the analogous binaphthyl phosphites, the absolute configuration of the product depends on the absolute configuration of the binaphtyl moiety of the ligand: the opposite prevailing enantiomer is obtained when using **2a** instead of **2b** (entries 1 and 3). This result points out a different asymmetric induction mechanism for the catalytic precursors **2a-b** with respect to those obtained from the analogous phosphites.[17] Having established that **2b** gave the better enantioselectivities, optimization of the reaction conditions was carried out using this catalytic precursor. Changing the base from Cs_2CO_3 to CsF did not affect at significant extent the yield as well as the enantioselectivity of the reaction both at 40° C and rT (entries 5 and 6). Similar results

were obtained by changing the reaction solvent. The use of ethereal solvents, such as tetrahydrofuran or dimethoxyethane, gave good yields of the cross-coupling product, in lesser reaction times (entries 7 and 8). It is conceivable that the coordinating solvent, THF or DME, can displace one ligand of the complex, giving rise to a monoligated species, which results slightly more active than the original complex,[17] but not more enantioselective. This species is less hindered and this can justify the higher reaction rate observed in coordinating solvents. Increasing the substrate concentration, in toluene as a solvent, had no influence on the enantioselectivity of the reaction (entries 4 and 9), but a higher reaction rate was observed, which gave complete conversion of the substrate at rT in only 16 hours (entry 9). The increased rate allowed to carry out the reaction at lower temperature (entry 10), so reaching the highest ee value of the product.

The optimized reaction conditions were used to screen different aryl bromides and different arylboronic acids in the reaction: the results are collected in Table 3.

When the reactions were performed at 0° C higher enantioselectivities than at rT were observed (entries 1 and 2, 6 and 7). However, as a consequence of the lower temperature the reaction slowed down and longer reaction times were required in order to obtain satisfactory yields of the products. At low temperatures, the arylboronic acids and the aryl bromides were less soluble, leading in some cases to low yields of the products (entries 5, 7, 12 and 14).

Table 3: Asymmetric Suzuki–Miyaura cross-coupling with complex **2b**[1]

Run	ArBr	$ArB(OH)_2$	Ar-Ar	T	t(h)	Yield%[2]	ee%[3]	AC[4]
1	**3a**	**4a**	**5a**	rT	16	95	25	(+)
2	**3a**	**4a**	**5a**	0° C	48	94	36	(+)
3	**3a**	**4b**	**5b**	rT	24	85	racemic	
4	**3a**	**4c**	**5d**	rT	18	90	10	(-)
5	**3a**	**4c**	**5d**	0° C	48	25[5]	12	(-)
6	**3b**	**4c**	**5c**	rT	48	56[5]	51	(-)
7	**3b**	**4c**	**5c**	0° C	72	35[5]	70	(-)
8	**3b**	**6c**	**7a**	rT	48	95	13	(R)
9	**3b**	**4a**	**5e**	0° C	72	75[5]	13	(-)
10	**3c**	**6a**	**7b**	rT	48	94	52	(S)
11	**3a**	**6b**	**7c**	0° C	24	95	31	(R)
12	**8a**	**6a**	**5a**	0° C	18	32[5]	40	(+)
13	**3a**	**6c**	**7b**	rT	48	88 (75[5])	17	(S)
14	**3a**	**6c**	**7b**	0° C	72	38[5]	19	(S)

1. All the reactions were stopped at complete substrate conversion or when it did not proceed further
2. NMR yield
3. Enantiomeric excess (ee) determined by enantioselective HPLC (for conditions see experimental)
4. Sign of the specific rotation of the sample or absolute configuration of the prevailing enantiomer, based on the elution order by comparison with the literature data.
5. Isolated yield

It is difficult to find a dependence of the outcome of the reaction only on the structural characteristics of the aryl bromide, as well as only on those of the aryl boronic acid: as a matter of fact, both reaction rate and enantioselectivity seem dependent on the combination aryl bromide – arylboronic acid. The 2-tolyl boronic acid **4a** gave a significantly lower reaction rate when coupled with **3b** (entry 9) than with **3a** (entry 2), but **3a** gave faster reactions when coupled with **4b**, **4c** and **6b** (entries 3, 4 and 11) than with **6c** (entries 13 and 14). The reaction between **3a** and **6b**, the aryl boronic acid devoid of substituent, was the fastest one, giving at 0° C 95% yield of the product in only 24 hours of reaction (entry 11), suggesting that the steric hindrance near the boronic group can reasonably account for the reaction rate. At the same time different enantioselectivities of the reaction were observed using the same aryl bromide (entries 1, 3, 4, 13) or the same aryl boronic acid (entries 2 and 9 or 5 and 7). The presence of a methoxy group near to the boronic moiety increases the enantioselectivity when the cross-coupling involves a 2-methyl substituted aryl bromide (entries 7, 12): the highest value of ee is obtained with one of these combinations, when 2-methoxyphenyl boronic acid was reacted with 1-bromo-2-methylnaphthalene at 0° C (entry 7). The reaction of 2-bromotoluene with 2-methoxy-1-naphthyl boronic acid (entry 12), a similar combination, gave a product in a lower ee, suggesting that also the size of the aryl moiety of the aryl boronic acid plays an important role in determining the extent of the enantioselectivity. The ees of the products were still satisfactory when the 2-methoxy substituted aryl boronic acid is coupled with an aryl bromide where the methyl group is at the 4-position (entry 10), whereas the opposite combination, where the methoxy group was on the aryl bromide gave the same product but in very low ee (entries 13 and 14). The presence of a methoxy group both at the position 2 of the aryl bromide and the arylboronic acid resulted detrimental for the enantioselectivity of the cross-coupling (entries 4 and 5), as well as the presence of a methyl group at the same position on both the reactants (entry 9). The reaction exhibited a modest enantioselectivity also when the 1-naphthyl boronic acid **6b**, devoid of substituent on the aryl moiety, is coupled with the 2-methoxy-1-bromonaphthalene **3a** (entry 11). By contrast the presence of a methyl group at the 4 position of the 1-naphthyl boronic acid (entries 8, 13, 14) or a formyl group at the position 2 of the aryl boronic acid (entry 3) was detrimental for the enantioselectivity of the reaction. It is to note that when the same cross-coupling product is prepared with the opposite combination of aryl bromide and aryl boronic acid (entries 2 and 12, 10 and 13) the same absolute configuration of the prevailing enantiomer is obtained in the presence of quite different yields (entries 2 and 12) and ees (entries 10 and 13). The different combination seems to influence the reaction rate or the extent of asymmetric induction but not its sense, which remains the same.

CONCLUSIONS

Pd(II) complexes of deoxycholic acid derived binaphthyl diamido phosphites have proven to work as chiral catalyst in the asymmetric Suzuki-Miyaura cross-coupling of aryl bromides with aryl boronic acids. A matched relationship between the stereochemistry of the bile acid and the (R) absolute configuration of the binaphthyl diamido phosphite moiety was observed, and complex **2b** gave better enantioselectivities. This complex displayed high activity allowing the reactions to be performed at 0 °C, where the products were obtained in moderate to very good yields and ees up to 70%.

EXPERIMENTAL

General

TLC analyses were performed on 60 F254 plates (0,2 mm) and chromatography purifications were carried out with silica gel (230- 400 mesh) or with neutral alumina (Brockmann I). All the reactions involving sensitive compounds were carried out under dry N_2, in flame-dried glassware. Toluene was refluxed over sodium-benzophenone and distilled before the use. n-Hexane, THF and DME were refluxed over potassium-benzophenone and distilled before the use. Dichloromethane, triethylamine and pyridine were refluxed over CaH_2 and distilled before the use. PCl_3 was distilled and dried with *freeze-pump-thaw* method before the use. Unless otherwise specified, the other compounds were commercially available and used as received. Methyl-3-acetyl-deoxycholan-24-ate was obtained as described previously and matched the reported characteristics.[18h]

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded in $CDCl_3$ or benezene-d_6, on a a Bruker AV-400 spectrometer (400.16 MHz for 1H) and the temperature was controlled to ± 0,1 °C. ^{1}H and ^{13}C NMR chemical shifts (ppm) are referred to TMS as external standard, ^{31}P NMR chemical shifts (ppm) are referred to H_3PO_4 as external standard: the following abbreviations are used: singlet (s), doublet (d), double of doublets (dd), double double doublet (ddd), double triplet (dt), triplet of doublets (td), triplet (t), multiplet (m), broad (br). Enantiomeric excesses were determined by HPLC analysis on chiral stationary phase, using Chiracel OD-H and OJ as columns with hexane or hexane/ ^{i}PrOH mixtures as a mobile phase and UV detection at 230 or 254 nm. Elemental analyses were obtained using an Elementar Vario MICRO cube equipment.

General Procedure for the synthesis of diamido phosphites

To a solution of methyl-3-acetyl-deoxycholan-24-ate (0.400 g, 0.9 mmol) in dry dichlorometane (5 ml) PCl_3 (0.24 ml, 2.7 mmol) was added under inert atmosphere, and the reaction mixture was stirred at room temperature for 24 h. After removing the solvent under reduced pressure, the crude

product was dissolved in dry toluene (2.5 ml) and a solution of N,N'-dimethyl-binaphtyldiamine (0.234 g, 0.75 mmol) and triethylamine (0.38 ml, 2.7 mmol) in dry toluene (2 ml) was dropwise added to this. After the addition, the reaction mixture was refluxed overnight. The mixture was cooled to room temperature and, after adding dry hexane (5 ml), was filtered under inert atmosphere: the filtrate was concentrated under vacuum and the crude product was purified by filtration under inert atmosphere on a pad of neutral Al_2O_3 (3 g in a 2.5 cm diameter column) using dry dichloromethane as eluent, obtaining the pure diammido phosphite as a white amorphous solid.

Methyl-3α-acetyl-12α-[(S)-N,N-dimethylbinaphthyl]diazaphospholidine-5β-cholan-24-ate, 1a

0.382 g (0.48 mmol, 55 %)

^{1}H NMR (400 MHz, 298 K, C_6D_6), δ: 7.78 (d, $^3J_{HH}$=8.1 Hz, c'), 7.76 (d, $^3J_{HH}$=8.5 Hz, b'), 7.72 (d, $^3J_{HH}$=8.5 Hz, 1H, b), 7.68 (d, $^3J_{HH}$=8.1 Hz, 1H, c), 7.50 (d, $^3J_{HH}$=8.8 Hz, 1H, a),7.41 (d, $^3J_{HH}$=8.5 Hz, 1H, a'), 7.36 (dd, $^3J_{HH}$=8.8 Hz, $^4J_{HH}$=0.9 Hz, f'), 7.29 (dd, $^3J_{HH}$=8.9 Hz, $^4J_{HH}$=0.8 Hz, 1H, f), 7.19 (ddd, $^3J_{HH}$=8.1, 6.9 Hz, $^4J_{HH}$=0.9 Hz, d'), 7.15 (ddd, $^3J_{HH}$=8.1, 6.8 Hz, $^4J_{HH}$=0.8 Hz, d), 6.93 (ddd, $^3J_{HH}$=8.9, 6.8 Hz, $^4J_{HH}$=1.2 Hz, e), 6.91 (ddd, $^3J_{HH}$=8.8, 6.9 Hz, $^4J_{HH}$=1.2 Hz, e'), 4.72 (m, 1H, 3), 4.28 (dt, $^3J_{HP}$=7.8 Hz, $^3J_{HH}$=2.6 Hz, 1H, 12), 3.40 (s, 3H, OCH_3), 2.92 (d, $^3J_{HP}$=9.1 Hz, 3H, NMe), 2.89 (d, $^3J_{HP}$=13.2 Hz, 3H, NMe'), 2.24 (m, 1H, 23), 2.14 (m, 1H, 23), 1.96-1.78 (m, 6H, 1, 2/4, 8/9, 16, 17, 22), 1.76-1.56 (5H, 2', 4', 11, 6/7, 14), 1.51 (s, 3H, HCH_2(C=O)), 1.49-1.00 (m, 12H), 0.98 (d, $^3J_{HH}$=6.7 Hz, 3H, 21), 0.63 (s, 3H, 19), 0.82 (s, 3H, 18)

^{13}C{^{1}H} NMR (100 MHz, 298 K, C_6D_6), δ: 173.9 (24), 169.5 (C=O), 145.8 (d, J_{CP}=7.5 Hz, h/i), 143.2 (d, $^5J_{CP}$=6.4 Hz, h'/i'), 133.8 (m), 133.4 (m'), 132.0 (g'), 131.6 (g), 129.3 (b), 128.52(b'), 128.46 (b'), 128.4 (c), 128.3 (d), 127.9 (f'), 127.3 (f), 126.2 (e), 126.1 (e'), 125.1 (d'), 124.2 (a'), 122.2 (a), 77.0 (d, $^2J_{CP}$=7.1 Hz, 12), 73.8 (3), 50.9 (OCH_3), 48.4 (14), 46.2 (17), 42.0 (5), 38.1 (d, $^2J_{CP}$=44.9 Hz, NMe'), 36.3 (20), 36.1 (d, $^2J_{CP}$=23.2 Hz, NMe), 35.9 (8/9), 35.2 (1), 34.2 (8/9), 32.5(2/4), 31.3 (22), 31.1 (23), 27.9 (16), 27.8 (d, $^5J_{CP}$=5.2 Hz, 11), 27.5 (2/4), 27.3 (15), 26.9 (6/7), 24.4 (6/7), 23.2 (18), 21.0 (s, Me(C=O)), 18.2 (d, $^6J_{CP}$=9.6 Hz, 21), 12.9 (19)

^{31}P{^{1}H} NMR (161 MHz, 298 K, C_6D_6), δ: 168.8.

Anal. Calcd. For $C_{49}H_{61}N_2O_5P$: C, 74.59; H, 7.79; N, 3.55. Found: C, 74.71; H, 7.76; N, 3.54.

Methyl-3α-acetyl-12α-[(R)-N,N-dimethylbinaphthyl]diazaphospholidine-5β-cholan-24-ate, 1b

0.313 g (0.40 mmol, 45 %). $[\alpha]_D^{25}$= -198 (c 0.1, CH_2Cl_2)

^{1}H NMR (400 MHz, 298 K, C_6D_6), δ: 7.95 (d, $^3J_{HH}$=8.6 Hz, b), 7.80-7.68 (m, 4H, a', b', c, c'), 7.66 (d, $^3J_{HH}$=8.6 Hz, a), 7.43 (d, $^3J_{HH}$=8.7 Hz, 1H, f), 7.40 (d, $^3J_{HH}$=8.5 Hz, f'), 7.20-7.10 (m, 2H, d, d'), 6.99-6.87 (m, 2H, e, e'), 4.91 (m, 1H, 3), 4.35 (br s, 1H, 12), 3.40 (s, 3H, OCH_3), 3.03 (d, $^3J_{HP}$=7.6

Hz, 3H, NMe'), 2.83 (d, $^3J_{HP}$=12.5 Hz, 3H, NMe**),** 2.23 (m, 2H, 23,23'), 2.18-2.06 (m, 3H, 8,6,11), 2.01-1.59 (m, 9H, 1,17,9,2,2',22,4,7,14), 1.81 (s, 3H, CH_3C=O), 1.60-0.86 (m, 11H, 4',15,15',20,16,16',5,22', 11',1',7',6'), 1.00 (d, $^3J_{HH}$=6.5 Hz, 3H, 21), 0.82 (s, 3H, 18), 0.62 (s, 3H, 19).

$^{13}C\{^1H\}$ NMR (100 MHz, 298 K, C_6D_6), δ: 173.5 (24), 169.7 (C=O), 145.4 (d, J_{CP}=7.3 Hz, ì'), 143.0 (d, $^5J_{CP}$=6.7 Hz, i), 133.5 (g'), 133.1 (g), 131.8 (l'), 131.7 (l), 131.3 (h), 131.0 (h'), 129.1 (b'), 128.3 (b), 128.1 (c), 128.0 (c'), 127.5 (f), 127.1 (f'), 125.9 (e), 125.8 (e'), 124.8 (d), 124.7 (a), 124.5 (d'), 123.7 (a'), 77.5 (d, $^2J_{CP}$=14 Hz, 12), 73.8 (3), 50.7 (OCH_3), 47.9 (14), 47.1 (13), 46.2 (17), 41.6 (5), 38.0 (d, $^2J_{CP}$=43.0 Hz, NMe), 36.0 (20), 35.8 (d, $^2J_{CP}$=20.0 Hz, NMe'), 35.1 (1), 34.3 (10), 33.3 (9), 32.3 (4), 31.1 (23), 30.9 (22), 29.8 (8), 27.8 (7), 27.0 (2), 26.8 (6), 26.4 (d, $^5J_{CP}$=12.0 Hz, 11), 26.3 (16), 24.0 (15), 22.7 (18), 20.8 (Me(C=O)), 17.4 (21), 12.4 (19).

$^{31}P\{^1H\}$ NMR (161 MHz, 298 K, C_6D_6), δ: 159.4

Anal. Calcd. for $C_{49}H_{61}N_2O_5P$: C, 74.59; H, 7.79; N, 3.55. Found: C, 74.50; H, 7.81; N, 3.56.

General procedure for the synthesis of complexes $PdCl_2L_2$

A solution of the ligand (0.5 mmol) in dry toluene (8 mL) was added to a red solution of $PdCl_2(PhCN)_2$ (0.25 mmol) in dry toluene (20 mL), which turned from red to yellow-orange. After 15 min stirring, the solvent was removed under reduced pressure and the yellow-orange solid was washed with n-hexane (3 x 4 mL) then dried under vacuum.

$PdCl_2(1a)_2$, 2a

850 mg (0.48 mmol, 96%) $[\alpha]_D^{31}$= -211 (c 0.89, CH_2Cl_2)

^1H NMR (400 MHz, 298 K, C_6D_6), δ: 8.44 (d, $^3J_{HH}$= 9.0 Hz, 1H, a), 8.04 (d, $^3J_{HH}$= 9.0 Hz, 1H, b), 7.66 (d, $^3J_{HH}$= 8.2 Hz, 1H, f'), 7.64 (d, $^3J_{HH}$= 8.9 Hz, 1H, b'), 7.53 (d, $^3J_{HH}$= 8.9 Hz, 1H, a'), 7.51 (d, $^3J_{HH}$=7.9 Hz, 1H, c), 7.21 (d, $^3J_{HH}$=8.4 Hz, 1H, c'), 7.15 (dd, $^3J_{HH}$= 8.2, 7.2 Hz, 1H, e'), 7.07 (d, $^3J_{HH}$= 8.8 Hz, 1H, f), 6.95 (dd, $^3J_{HH}$= 7.9, 6.9 Hz, 1H, d), 6.84 (dd, $^3J_{HH}$=8.4, 7.2, 1H, d'), 6.73 (dd, $^3J_{HH}$= 8.8, 6.9 Hz, 1H, e), 4.78 (m, 1H, 12), 4.56 (m, 1H, 3), 3.99 (t, $^3J_{HP}$=6.2 Hz, 3H, NMe), 3.67 (t, $^3J_{HP}$=5.9 Hz, 3H, NMe'), 3.43 (s, 3H, OCH_3), 3.01 (q, $^3J_{HH}$=9.6 Hz, 1H, 17), 2.60 (m, 1H, 23), 2.44 (m, 1H, 23), 2.07-0.62 (m, 27H), 1.57 (d, $^3J_{HH}$=6.3 Hz, 21), 0.58 (s, 3H, 19), 0.47 (s, 3H, 18), 0.04 (td, $^2J_{HH}$=14.4 Hz, $^3J_{HH}$=2.8 Hz, 1H, 1), -0.20 (d, $^2J_{HH}$=14.4 Hz, 1H, 1)

$^{13}C\{^1H\}$ NMR (100 MHz, 298 K, C_6D_6), δ: 174.0 (24), 169.4 (C=O), 133.7 (g), 133.5 (g'), 131.8 (h), 131.7 (h'), 129.6 (b), 128.6 (b', c, c'), 127.6 (f'), 127.3 (f), 126.6 (d'), 126.4 (e), 126.0 (e'), 124.8 (d), 123.2 (a'), 122.2 (a), 82.8 (t, $^2J_{cP}$=6.8 Hz, 12), 73.8 (3), 51.1 (OCH_3), 47.5 (14), 46.4 (17), 41.7 (5), 40.8 (t, $^2J_{CP}$=10.6 Hz, NMe'), 38.2 (t, $^2J_{CP}$=5.8 Hz, NMe), 36.0 (8/9), 35.9 (20), 34.9

(9/8), 34.2 (1), 32.6 (4), 32.2 (23), 31.7 (22), 27.43 (16), 27.37 (6/7), 26.3 (7/6), 25.8 (2), 24.2 (15), 23.0 (11), 22.6 (18), 21.2 (CH_3(C=O)), 18.9 (21), 12.8 (19)

$^{31}P\{^1H\}$ NMR (161 MHz, 298 K, C_6D_6), δ: 117.1

Anal. Calcd. for $C_{98}H_{122}Cl_2N_4O_{10}P_2Pd$: C, 67.06; H, 7.01; N, 3.19. Found: C, 66.98; H, 6.99; N, 3.18.

$PdCl_2$(1b)$_2$, 2b

810 mg (0.46 mmol, 92%). $[\alpha]_D^{25}$= +273 (c 1, CH_2Cl_2)

^1H NMR (400 MHz, 298 K, C_6D_6), δ: 8.58 (d, $^3J_{HH}$= 8.8 Hz, 1H, a'), 8.28 (d, $^3J_{HH}$= 8.7 Hz, 1H, b), 8.15 (d, $^3J_{HH}$= 8.7 Hz, 1H, a), 8.07 (d, $^3J_{HH}$= 8.8 Hz, 1H, b'), 7.91 (d, br.s., 1H, c'), 7.68 (d, $^3J_{HH}$=8.2 Hz, 1H, c), 7.30 (d, $^3J_{HH}$=8.3 Hz, 1H, f), 7.27 (d, $^3J_{HH}$= 8.8 Hz, 1H, f'), 7.18 (t, $^3J_{HH}$= 7.4 Hz, 1H, d'), 7.07 (ddd, $^3J_{HH}$= 8.2, 6.9, 1.0 Hz, 1H, d), 6.91 (t, $^3J_{HH}$=7.4, Hz 1H, e'), 6.83 (ddd, $^3J_{HH}$= 8.3, 6.9, 1.2 Hz, 1H, e), 6.16 (br.s., 1H, 12), 4.94 (m, 1H, 3), 3.58 (t, $^3J_{HP}$=4.6 Hz, 3H, NMe), 3.51 (t, $^3J_{HP}$=6.0 Hz, 3H, NMe'), 3.46 (s, 3H, OCH_3), 3.51 (m, 1H, 11), 2.51 (m, 1H, 23), 2.32 (m, 1H, 23'), 2.20-1.79 (m, 6H, 22,22',17,2,2',9), 1.76 (s, 3H, CH_3C=O), 1.75-1.61 (m, 3H, 1,4,11'), 1.64 (d, 1H, $^3J_{HH}$=4.0 Hz, 21), 1.61-1.01 (m, 10H, 4',1',5,6,8, 14,15,16,16',20), 0.90-0.78 (m, 4H, 7,7',15',6') 0.69 (s, 3H, 19), 0.54 (s, 3H, 18)

$^{13}C\{^1H\}$ NMR (100 MHz, 298 K, C_6D_6), δ: 174.2 (24), 170.2 (C=O), 143.1 (i/i'), 142.8 (i/i'), 133.8 133.3, 133.2, 133.1 (g/g'/h/h'), 129.5, 129.4 (l/l'), 129.2 (b'), 129.1 (b), 129.0 (a'), 128.6 (c), 128.5 (c'), 127.9 (f), 127.7 (a), 127.5 (f'), 126.4 (e), 126.2 (e'), 126.1 (d), 125.5 (d'), 81.2 (12), 74.6 (3), 51.2 (OCH_3), 47.2 (17), 47.2 (13), 46.7 (14), 42.7 (NMe'), 42.4 (5), 40.3(NMe), 37.7 (20), 36.8 (8), 35.5 (9), 33.6 (4), 32.8 (23), 32.0 (10), 31.1 (22), 30.4 (11), 29.1 (1), 28.6 (2), 28.2 (16), 26.8 (15), 24.8 (6), 23.2 (18), 22.6 (18), 21.2 (CH_3(C=O)), 18.8 (21), 13.1 (19).

$^{31}P\{^1H\}$ NMR (161 MHz, 298 K, C_6D_6), δ: 115.8

Anal. Calcd. for $C_{98}H_{122}Cl_2N_4O_{10}P_2Pd$: C, 67.06; H, 7.01; N, 3.19. Found: C, 67.12; H, 7.02; N, 3.18.

General procedure for Suzuki-Miyaura cross coupling reaction

A flame dried Schlenk was charged, under inert atmosphere, with aryl bromide (0.5 mmol), aryl boronic acid (0.75 mmol) and **2b** (0.025 mmol, 5 mol %) dissolved in dry toluene (5 ml), then Cs_2CO_3 (1.25 mmol) was added. The mixture was stirred at room temperature or 0 °C, until TLC analysis (hexane–CH_2Cl_2 8:2) showed complete substrate conversion or when it did not proceed further. The reaction was quenched with NH_4Cl solution, extracted with diethyl ether (3 x 10 mL) and the organic phase was dried over anhydrous Na_2SO_4. After removing the solvent at reduced

pressure, the crude product was directly analysed by ^{1}H NMR and, if necessary, purified by column chromatography (SiO_2; hexane–CH_2Cl_2 8:2). The ee of the biaryl products were determined by HPLC on a chiral stationary phase.

(+)-2-Methoxy-1-(2-methylphenyl)-naphthalene,[19] 5a

From ortho-tolylboronic acid and 1-bromo-2-methoxynaphthalene after 16h at RT.

^{1}H NMR (400 MHz, 298 K, $CDCl_3$), δ: 7.90 (d, 1H, J_{HH} = 9.2 Hz), 7.86–7.81 (m, 1H), 7.36–7.20 (m, 7H), 7.17 (d, 1H, J_{HH} = 5.0 Hz), 3.83 (s, 3H), 1.98 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, 298 K, $CDCl_3$), δ: 153.6, 137.6, 136.1, 133.4, 130.8, 129.8, 128.9, 127.8. 127.5, 126.3, 125.6, 125.0, 124.5, 123.4, 113.6, 56.5, 19.7.

HPLC: (Chiracel OJ, hexane/2-propanol 99:1, 1.0 mL/min, T = 25 °C, λ = 230 nm): t_1= 8.4 min (major), t_2= 11.5 min (minor).

2-Methoxy-1-(2-formylphenyl)-naphthalene,[17] 5b

From 1-bromo-2-methoxynaphthalene and 2-formylphenylboronic acid after 24h at rT.

^{1}H NMR (400 MHz, 298 K, $CDCl_3$), δ: 9.64 (s, 1H), 8.15 (dd, 1H, J_{HH} = 7.5, 3.9 Hz), 7.99 (d, 1H, J_{HH} = 9 Hz), 7.74 (t, 1H, J_{HH} = 7.5 Hz), 7.66 (dd, 1H, J_{HH} = 9.6 Hz, 3.3 Hz) 7.59 (t, 1H, J_{HH} = 6.9 Hz), 7.41–7.33 (m, 5H), 3.84 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, 298 K, $CDCl_3$), δ: 192.8, 154.4, 140.6, 135.3, 134.1, 133.9, 132.6, 130.6, 129.2, 128.3, 128.2, 127.2, 125.1, 124.1, 120.3, 113.0, 56.6.

HPLC (Chiralcel OJ, hexane/2-propanol 99:1 1.0 mL/min, T = 25 °C, λ = 230 nm): t_1= 20.1 min (major), t_2= 26.9 min (minor).

(-) 2-Methyl-1-(2-methoxyphenyl)-naphthalene, 5c

From 1-bromo-2-methylnaphthalene and 2-methoxyphenyl boronic acid, after 48h at rT the reaction mixture was purified giving 70 mg (0.28 mmol, 56%) of 2-methyl-1-(2-methoxyphenyl)-naphthalene. $[\alpha]_D^{25}$= -3 (c 1, $CHCl_3$) for a sample having 51% ee.

^{1}H NMR (400 MHz, 298 K, $CDCl_3$), δ: 7.89 (d, 1H, J_{HH} = 8.0 Hz), 7.84 (d, 1H, J_{HH} = 8.0 Hz), 7.52-7.33 (m, 5H), 7.24-7.08 (m, 3H), 3.73 (s, 3H), 2.29 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, 298 K, $CDCl_3$), δ: 157.4, 134.7, 133.9, 132.9, 132.0, 131.8, 128.8, 128.5, 128.3, 127.8, 127.2, 125.9, 125.7, 124.6, 120.7, 111.2, 55.5, 20.6.

HPLC (Chiracel OJ, hexane:2-propanol 99.5:0.5, 0.7 ml/min, 230 nm) t_1= 10.0 min (major), t_2=14.1 min (minor).

Anal. Calcd. for $C_{18}H_{16}O$: C, 87.06; H, 6.49. Found: C, 86.98; H, 6.48.

(-) 2-Methoxy-1-(2-methoxyphenyl)-naphthalene,[17] 5d

From 1-bromo-2-methoxynaphthalene and 2-methoxyphenylboronic acid after 48 h at 0 °C, the reaction mixture was purified by column chromatography giving 33 mg (0.125 mmol, 25%) of 2-methoxy-1-(2-methoxyphenyl)-naphthalene as a white solid.

^{1}H NMR (400 MHz, 298 K, $CDCl_3$), δ: 7.88 (d, 1H, J_{HH} = 9.0 Hz), 7.80 (m, 1H), 7.45–7.28 (m, 5H), 7.21 (dd, 1H, J_{HH} = 7.2 Hz, 1.8 Hz), 7.07 (m, 2H), 3.84 (s, 3H), 3.70 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, 298 K, $CDCl_3$), δ: 157.9, 154.4, 133.8, 132.5, 129.2, 128.9, 127.9, 126.2, 125.6, 125.4, 123.5, 122.4, 120.7, 114.4, 111.5, 108.0, 57.2, 55.9.

HPLC (Chiralcel OJ, hexane/2-propanol 99:1 1.0 mL/min, T = 25 °C, λ = 230 nm): t_1=16.4 min (minor), t_2=21.7 min (major).

(-) 2-Methyl-1-(2-methylphenyl)-naphthalene,[20] 5e

From 1-btomo-2-methylnaphthalene and 2-tolyl boronic acid, after 72h at 0 °C the reaction mixture was purified by column chromatography giving 87 mg (0.37 mmol, 75%) of 2-Methyl-1-(2-methylphenyl)-naphthalene.

^{1}H NMR (400 MHz, 298 K, $CDCl_3$), δ: 7.89 (d, J_{HH} = 8.1 Hz, 1H), 7.83 (d, J_{HH} = 8.4 Hz, 1H), 7.50–7.24 (m, 7H), 7.17 (d, J_{HH} = 7.0 Hz, 1H), 2.21 (s, 3H), 1.96 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, 298 K, $CDCl_3$), δ: 139.2, 137.5, 136.8, 133.1, 132.6, 132.0, 130.0, 128.6, 127.8, 127.4, 127.1, 126.0, 125.9, 125.7, 124.8, 20.3, 19.5.

HPLC (Chiracel OJ, hexane, 0.5 ml/min, T = 25 °C, 254 nm): t_1= 12.5 min (major), t_2=19.5 min (minor).

(R)-2,4'-Dimethyl-1,1'-binaphthyl,[14] 7a

From 1-bromo-2-methylnaphthalene and 4-methyl-1-naphthaleneboronic acid, after 48h at rT.

^{1}H NMR (400 MHz, 298 K, $CDCl_3$), δ: 8.10 (d, 1H, J_{HH} = 9.3 Hz), 7.89 (d, 1H, J_{HH} = 8.1 Hz), 7.87 (d, 1H, J_{HH} = 8.4 Hz), 7.57–7.15 (m, 9H), 2.83 (s, 3H), 2.13 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, 298 K, $CDCl_3$), δ: 136.5, 135.9, 134.6, 134.0, 133.8, 133.0, 132.8, 132.2, 128.7, 127.9, 127.6, 126.8, 126.6, 126.5, 126.0, 125.9, 125.8, 124.9, 124.6, 20.7, 19.7.

HPLC (Chiracel OJ, hexane/2-propanol 90:10, 1.0 mL/min, T = 25 °C, λ = 230 nm): t_1 = 4.7 min (major) and t_2 = 15.3 min (minor).

(S)-2-Methoxy-4'-methyl-1,1'-binaphthyl,[14] 7b

From 1-bromo-4'-methylnaphthalene and 2-methoxy-1-naphthaleneboronic acid, after 48h at rT.

^{1}H NMR (400 MHz, 298 K, $CDCl_3$), δ: 7.92 (d, 1H, J_{HH} = 9.2 Hz), 7.86 (m, 1H),7.41–7.26 (m, 9H), 7.21 (m, 1H), 3.80 (s, 3H), 2.85 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, 298 K, $CDCl_3$), δ: 154.8, 134.6, 134.0, 133.1, 133.0, 132.9, 129.5, 128.2, 127.9, 126.9, 126.6, 126.5, 125.8, 125.7, 125.6, 124.5, 123.7, 114.0, 56.9, 19.8.

HPLC (Chiracel OJ, hexane/2-propanol 90:10, 1.0 mL/min, T = 30 °C, λ = 227 nm): t_1 = 7.2 min (major) and t_2 = 29.3 min (minor).

(R)-2-Methoxy-1,1'-binaphthyl,[14] 7c

From 1-bromo-2-methoxynaphthalene and 1-naphthaleneboronic acid after 24 h at 0 °C.

^{1}H NMR (400 MHz, 298 K, $CDCl_3$), δ: 8.01–7.90 (m, 3H), 7.87 (d, 1H, J_{HH} = 8.1 Hz), 7.62 (t, 1H, J_{HH} = 6 Hz), 7.48–7.41 (m, 3H), 7.35–7.13 (m, 5H), 3.75 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, 298 K, $CDCl_3$), δ: 154.8, 134.7, 134.4, 133.8, 133.1, 129.6, 129.2, 128.6, 128.4, 127.9, 127.8, 126.5, 126.3, 126.0, 125.8, 125.7, 125.6, 123.7, 123.4, 114.0, 56.9.

HPLC (Chiracel OJ, hexane/2-propanol 95:5, 1.0 mL/min, T = 25 °C, λ = 230 nm): t_1= 10.2 min (major) and t_2 = 15.7 min (minor).

SUPPLEMENTARY DATA

Supplementary data (NMR spectra and 2D maps of all new compounds and HPLC chromatograms)

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