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Asymmetric Suzuki cross-coupling reaction: chirality reversal depending on the palladium–chiral phosphine ratio

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Abstract—Suzuki cross-coupling reaction with sterically hindered arylboronic acids is reported. Good yields are obtained by using DME and cesium fluoride in the presence of $Pd(OAc)_2$ and triphenylphosphine. The catalytic asymmetric reaction between 2-methoxy-1-naphthylboronic acid and 1-iodo-2-methoxynaphthalene was studied in the presence of a palladium–chiral phosphine catalyst. When the reaction was carried out with $Pd(OAc)_2$ and (*R*)-BINAP (versus (*R*)-TolBINAP), the enantioselection was dramatically influenced by the phosphine/palladium ratio. © 2002 Published by Elsevier Science Ltd.

1. Introduction

The biaryl subunit is the central building block of a large number of natural products and chiral biaryls are the backbone of many chiral ligands,[1] crown ethers,[2] chiral liquid crystals.[3] Due to their numerous applications, there is considerable interest in the development of efficient procedures which give enantiomerically pure biaryls. For this purpose, useful methods using stoichiometric chiral auxiliaries or chiral starting materials have been reported:[4] for example, binaphthalene derivatives were obtained with high selectivity through the use of chiral oxazoline by Meyers,[4b,4c] chiral leaving groups by Cram[4d,4e] or coupling by chiral copper complexes by Brussee.[4f]

In the last three decades, Pd(0)-catalyzed cross-coupling reactions[5] have emerged as a powerful tool for carbon–carbon bond formation and have offered an access to unsymmetrical biaryls with a wide range of structural diversity. For such couplings, the use of chiral ligands can lead to atrop-enantioselective synthesis as demonstrated by the pioneering work of Hayashi[6] who synthesized chiral biaryls by Ni- or Pd-catalyzed Kumada coupling. Among the Pd(0)-catalyzed coupling reactions, the Suzuki coupling[5] has gained particular attention. It consists of the reaction of an arylhalide (or a triflate) with a boronic acid in the presence of a base. The advantages of this procedure are numerous: the reaction occurs under mild conditions, tolerates a broad array of functional groups and yields non-toxic by-products. In addition, arylboron reagents are readily accessible substrates, unaffected by the presence of water or oxygen. Two strategies have been applied for the synthesis of chiral biaryls by Suzuki coupling. The first one, described by Uemura,[4j] consists of using chiral arene(chromium)halide complexes. In another strategy, the atroposelectivity is induced through the use of chiral catalyst. This was first illustrated in the total synthesis of Vancomycin by Nicolaou[7] who obtained a chiral biaryl with up to 55% diastereomeric excess by using a chiral ligand. During the completion of this work, enantioselective Suzuki couplings induced by chiral ligand were also reported by Cammidge[8] and Buchwald.[9]

To obtain configurationally stable chiral biaryls, at least three *ortho* substituents are usually necessary.[10] The usual Suzuki coupling procedure[11] using $Pd(PPh_3)_4$ and aqueous Na_2CO_3 in DME or benzene at 80°C works effectively for most of the arylboronic acids. However, sterically hindered[12] or electron-withdrawing group substituted[13] arylboronic acids never provide in these conditions satisfactory results due to steric hindrance or competitive hydrolytic deboronation. Furthermore, to obtain acceptable yields of hindered biaryls, high temperatures (80–110°C) are usually needed with multihour reaction times.[14] In atropoisomer selective reactions, these conditions would be deleterious to the discrimination between diastereomeric

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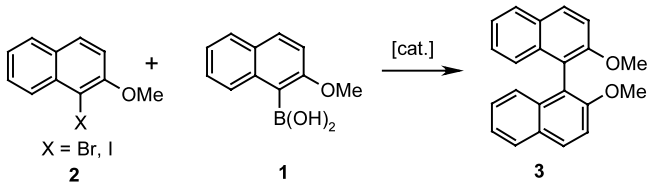
transition states and could also racemize the biaryls formed. Consequently, sterically hindered biaryl coupling has attracted considerable attention in recent years. Investigations at various temperatures and with different bases were developed and it was pointed out that addition of stronger bases[12] than Na_2CO_3, e.g. aqueous NaOH or $Ba(OH)_2$, exerts a remarkable effect on acceleration of the rate of coupling. Furthermore, Anderson[15] demonstrated that certain hindered biaryls can be formed in good yields via Suzuki coupling at room temperature with thallium(I) hydroxide in DMA. More recently, sodium phenoxide and silver carbonate[16] at reflux in benzene proved to be a useful alternative to the toxic thallium carbonate or hydroxide with sterically hindered boronic acids.

In connection with the study of asymmetric Suzuki coupling, we describe herein in the first part our results on the biaryl coupling between sterically hindered boronic acids and aryliodides showing that it is possible to get good to excellent yields and short reaction times. Then in the second part, we report studies on palladium-catalyzed asymmetric Suzuki coupling reaction between 2-methoxy-1-naphthylboronic acid **1** and 1-iodo-2-methoxy-naphthalene **2** (Scheme 1) using various chiral phosphine ligands. In the course of our investigation, we have found that the ratio of BINAP or TolBINAP to $Pd(OAc)_2$ influences dramatically the enantioselection.

2. Results and discussion

2.1. Suzuki cross-coupling reaction of sterically hindered arylboronic acid

We first explored the racemic coupling between 2-methoxy-1-naphthylboronic acid **1** and 1-bromo or 1-iodo-2-methoxynaphthalene **2** (Scheme 1) using



Scheme 1.

$Pd(PPh_3)_4$ or $Pd(OAc)_2$+3PPh_3. These coupling partners are especially congested and in addition 2-methoxy-1-naphthylboronic acid **1** is particularly sensitive to the hydrolytic deboronation.[17] 1-Iodo-2-methoxynaphthalene was synthesized from 2-methoxynaphthalene with *N*-iodosuccinimide in CH_3CN.[18] 1-Bromo-2-methoxynaphthalene was obtained by treatment of 1-bromo-2-naphthol with dimethylsulfate in presence of a phase transfer agent (Aliquat 336).[19] 2-Methoxy-1-naphthylboronic acid was synthesized by converting the corresponding bromide into its Grignard reagent, quenching with trimethylborate and aqueous acidic work-up.[20]

As shown in Table 1, preliminary experiments were carried out with the usual conditions for Suzuki coupling,[21] i.e. $Pd(PPh_3)_4$ as catalyst, Na_2CO_3 as base, toluene/ethanol/H_2O, 2/2/1 at reflux (80°C). No reaction occurred with the bromide and the protonolysis of the boronic acid was observed (Table 1, entry 1). In the presence of the iodide, the reaction took place in moderate yield depending on the amount of boronic acid: 40% yield with 1.6 equiv. of boronic acid after 16 h at 70°C and 50% with 2.2 equiv. (Table 1, entries 2 and 3). The cross-coupling reaction with $Pd(OAc)_2$ and triphenylphosphine (more easily handled than $Pd(PPh_3)_4$) occurred in 40% yield (Table 1, entry 4). Changing the solvent from toluene to DME increased the yield to 52%; however, the coupling in DMF was unsuccessful (Table 1, entries 5 and 6). Nevertheless, as reported in the literature,[12] $Ba(OH)_2$ in DME/H_2O led to the coupling product in 74% yield after 4 h at 70°C (Table 1, entry 7). At the same time, the homocoupling of 2-methoxy-1-naphthylboronic acid in the presence of O_2 in toluene without aqueous base[22] or in aqueous ethanol with Na_2CO_3[23] was performed. In each case we found only the product of deboronation and no trace of coupling product. Interestingly after 6 days in toluene without aqueous base, a small quantity of boronic acid was still present whereas after 36 h in aqueous ethanol the protonolysis of the boronic acid was completed. Therefore, we chose to run our reaction in anhydrous solvent without aqueous base. K_3PO_4 suspended in DME[12,24] seems to be a good alternative but the coupling product was isolated in only 45% yield (Table 1, entry 8).

Table 1. Preliminary experiments of the Pd-catalyzed Suzuki cross-coupling of 2-methoxy-1-naphthylboronic acid with 1-bromo or 1-iodo-2-methoxynaphthalene

Entry	X	Catalyst	Equiv. of boronic acid	Base	Solvent	Isolated yield (%)
1	Br	$Pd(PPh_3)_4$	1.0	Na_2CO_3	Toluene/EtOH/H_2O 2/2/1	0
2	I	$Pd(PPh_3)_4$	1.6	Na_2CO_3	Toluene/EtOH/H_2O 2/2/1	40
3	I	$Pd(PPh_3)_4$	2.2	Na_2CO_3	Toluene/EtOH/H_2O 2/2/1	50
4	I	$Pd(OAc)_2$, PPh_3	1.5	Na_2CO_3	Toluene/EtOH/H_2O 2/2/1	40
5	I	$Pd(OAc)_2$, PPh_3	1.9	Na_2CO_3	DMF/H_2O 2/1	0
6	I	$Pd(OAc)_2$, PPh_3	1.9	Na_2CO_3	DME/H_2O 1/1	52
7	I	$Pd(OAc)_2$, PPh_3	1.9	$Ba(OH)_2$	DME/H_2O 1/1	74
8	I	$Pd(OAc)_2$, PPh_3	2.0	K_3PO_4	DME	45

Reaction conditions: 7 mol% $Pd(PPh_3)_4$ or 10 mol% $Pd(OAc)_2$+30 mol% PPh_3, 5 equiv. of base, 16 h at 80°C.

In the Suzuki coupling reaction, the role of the base is to form the boronate anion which serves as nucleophile in the transmetallation step. Because of the high affinity of fluoride ion for boron,[25] fluorides should be especially suitable for this purpose. For our studies, we chose cesium fluoride, used by Wright for Suzuki coupling with arylbromides parasubstituted by aqueous base sensitive functional groups.[26]

The coupling reaction of 2-methoxy-1-naphthylboronic acid and 1-iodo-2-methoxynaphthalene was first performed in DME with 2.1 equiv. CsF per mol of boronic acid and the coupling product was isolated in 98% yield after 16 h at 70°C (Table 2, entry 1). Changing the solvent from DME to toluene gave the binaphthyl in 89% yield (Table 2, entry 2). Furthermore, using 3 equiv. CsF per mol of boronic acid increased the rate of the reaction. Actually the disubstituted binaphthyl was isolated in quantitative yield after 3 h at 70°C (Table 2, entry 3).

To develop this synthetic procedure and identify its scope and limitations, we studied the coupling of *o*-tolylboronic acid, mesitylboronic acid, 2,6-dimethoxyphenylboronic acid with iodobenzene, *o*-iodoanisole, *o*-iodotoluene, bromomesitylene and 1,3-dimethyl-2-iodobenzene using CsF as a base, 3 mol% of catalyst in anhydrous DME (Table 3).

Our route to substituted biaryls gave good to excellent results with sterically hindered boronic acids. Short reaction times at a temperature of 70°C led to good yields even for trisubstituted biaryl (Table 3, entries 3 and 4). As expected[12,15,26] *ortho*-*ortho*′-tetrasubstituted biaryls were obtained in much lower yields (Table 3, entries 5 and 6). No further evolution could be observed after 48 h.

2.2. Asymmetric Suzuki coupling

These coupling conditions were then applied to investigation of the asymmetric Suzuki synthesis of 2,2′-dimethoxy-1,1′-dinaphthalene **3** using various chiral ligands. The coupling reaction between 2-methoxy-1-naphthylboronic acid **1** and 1-iodo-2-methoxynaphthalene **2** (Scheme 1) was first carried out using about 10 mol% of $Pd(OAc)_2$ or 5 mol% of $(\eta^3\text{-allylPdCl})_2$ and various amounts of (*R*)-BINAP or (*R*)-TolBINAP as the ligand in DME at 70°C. When the ratio chiral phosphine/palladium was less than one, the binaphthyl compound (−)-**3** was obtained as the major enantiomer (Table 4, entries 1, 2, 7 and 9). However, when the ratio ligand/palladium was more than one, the enantioselection was reversed, thus (+)-**3** was obtained (Table 4, entries 3, 4, 5, 8 and 10). For example, the (+)-2,2′-dimethoxy-1,1′-dinaphthalene **3** was synthesized with a yield of 86% and ee of 29% for a ratio ligand/Pd equal to 1.28. Furthermore, according to the work of Amatore and Jutand,[27] an excess of ligand inhibited the coupling reaction (Table 4, entry 6).

To improve the enantioselectivity, we changed the solvent of the reaction and a small improvement was found in dioxane with a ratio (*R*)-BINAP/$(\eta^3\text{-allylPdCl})_2$ equal to 0.92, the (−)-**3** enantiomer was obtained in 30% ee and 76% yield (Table 4, entry 11).

The chirality reversal depending on the ratio ligand/Pd was first remarked by Genêt[28] in asymmetric allylic alkylation of Schiff bases with $Pd(dba)_2$ and (+)-NORPHOS or (+)-DIOP. He attributed this phenomena to a relative distribution of different structures of the catalyst. Furthermore, Shimizu[29] in asymmetric elimination of allylic carbonate with $Pd(OAc)_2$ and (*S*)-BINAP observed this effect of ligand-to-metal ratio. In this case, (*S*)-BINAP is used in combination with

Table 2. Effect of CsF on the Pd-catalyzed Suzuki cross-coupling of 2-methoxy-1-naphthylboronic acid with 1-bromo or 1-iodo-2-methoxynaphthalene

Entry	Equiv. of boronic acid	Base (equiv.)	Solvent	Reaction time (h)	Isolated yield (%)
1	2	CsF (4.3)	DME	16	98
2	2	CsF (4.2)	Toluene	16	89
3	1.5	CsF (4.6)	DME	3	100

Reaction conditions: 10 mol% $Pd(OAc)_2$+30 mol% PPh_3, anhydrous solvent.

Table 3. Scope of the sterically hindered Suzuki cross-coupling in the presence of CsF

Entry	Boronic acid	Iodide	Isolated yield (%)
1	*o*-Tolylboronic acid	Iodobenzene	86
2	Mesitylboronic acid	Iodobenzene	82
3	Mesitylboronic acid	*o*-Iodotoluene	75
4	Mesitylboronic acid	*o*-Iodoanisole	70
5	Mesitylboronic acid	Bromomesitylene	15
6	2,6-Dimethoxyphenylboronic acid	1,3-Dimethyl-2-iodobenzene	10

Reaction conditions: 3 mol% $Pd(OAc)_2$, 9 mol% PPh_3, 1.05 equiv. boronic acid, 3.15 equiv. CsF, 1.0 equiv. iodide in anhydrous DME, 6 h.

Table 4. Coupling reaction between 2-methoxy-1-naphthylboronic acid 1 and 1-iodo-2-methoxynaphthalene 2 using (*R*)-BINAP and (*R*)-TolBINAP

Entry	Pd	Solvent	Ligand	Ligand/Pd	Time (h)	Yield (%)	Ee[a] (%)	Rotation
1	$Pd(OAc)_2$[b]	DME	(*R*)-BINAP	0.53	12	27	14	(−)
2	$Pd(OAc)_2$[b]	DME	(*R*)-BINAP	0.85	6	84	22	(−)
3	$Pd(OAc)_2$[b]	DME	(*R*)-BINAP	1.28	6	86	29	(+)
4	$Pd(OAc)_2$[b]	DME	(*R*)-BINAP	1.55	3.5	85	24	(+)
5	$Pd(OAc)_2$[b]	DME	(*R*)-BINAP	1.85	4	94	28	(+)
6	$Pd(OAc)_2$[b]	DME	(*R*)-BINAP	3.1	6	19	20	(+)
7	$(\eta^3\text{-allylPdCl})_2$[c]	DME	(*R*)-BINAP	0.97	3	85	22	(−)
8	$(\eta^3\text{-allylPdCl})_2$[b]	DME	(*R*)-BINAP	2.00	3.5	79	26	(+)
9	$(\eta^3\text{-allylPdCl})_2$[c]	DME	(*R*)-TolBINAP	0.96	12	67	22	(−)
10	$(\eta^3\text{-allylPdCl})_2$[c]	DME	(*R*)-TolBINAP	1.93	7	50	24	(+)
11	$(\eta^3\text{-allylPdCl})_2$[b]	Dioxane	(*R*)-BINAP	0.92	7	76	30	(−)
12	$Pd_2(dba)_3$[b]	Dioxane	(*R*)-BINAP	1.1	7.5	46	15	(+)
13	$Pd_2(dba)_3$[b]	Dioxane	(*R*)-BINAP(O)	1.1	12	22	24	(+)
13	$Pd(OAc)_2$[b]	DME	(*R*)-BINAP(O)	2	12	31	14	(+)

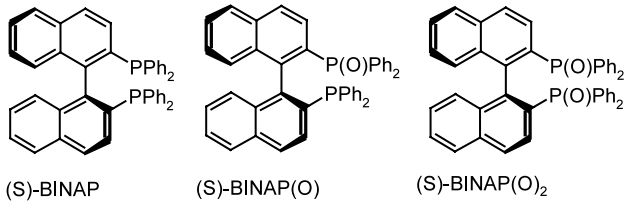
Reaction conditions: 2 equiv. boronic acid, 6 equiv. CsF, 70°C.

[a] Ees were determined from specific rotations or by ^{1}H NMR with Pirkle shift reagent 2,2,2-trifluoro-1-(9-anthryl)ethanol.[33]

[b] 10% Pd.

[c] 20% Pd.

$Pd(OAc)_2$ as catalyst precursor, then (*S*)-BINAP(O) and (*S*)-$BINAP(O)_2$ could be formed during the reduction of $Pd^{(2+)}$ to $Pd^{(0)}$,[30] (Scheme 2). Actually Shimizu showed that Pd(0)-(*S*)-BINAP and Pd(0)-(*S*)-BINAP(O) have opposite enantiomeric selectivities.



Scheme 2.

We then tried the coupling reaction with $Pd_2(dba)_3$ and (*R*)-BINAP(O)[31] (ratio ligand/Pd: 1.1) in dioxane, (+)-**3** was obtained with 24% ee instead of (+) 15% ee with (*R*)-BINAP (Table 4, entries 12 and 13). Another experiment was performed with $Pd(OAc)_2$ and (*R*)-BINAP(O) (ratio ligand/Pd: 2) in DME, (+)-**3** was obtained with 14% ee (Table 4, entry 13). These results indicate that in our case the presence of (*R*)-BINAP(O) does not explain this chirality reversal. More recently Burgess[32] described a similar effect of ligand-to-metal ratio in alkylation of allylic acetate with $(\eta^3\text{-allylPdCl})_2$ and phosphine oxazoline ligands. The explanation proposed was based on the formation of complexes with two phosphines coordinated to palladium when the ligand-to-metal ratio is greater than 1 instead of complexes with one P- and one *N*-ligating group when the ligand-to-metal ratio is less than 1. However, the exact structure of the active species are not known and as Genêt and also Burgess mentioned, we believe in the formation of several catalytically active structures such as di- or polynuclear complexes for understanding this enantioselective phenomena.

Then, several chiral bidentate ligands were tested. No reaction was observed by using (*R*,*R*)-DIOP, (*R*,*R*)-Me-DUPHOS or (*R*)-(*S*)-JOSIPHOS, respectively, combined with $Pd(OAc)_2$ or $Pd_2(dba)_3$. With (*S*,*S*)-CHIRAPHOS, the coupling occurred but a very low ee was obtained (Table 5, entries 1, 2 and 3). Here again the reversal of the optical activity of the dinaphthalene **3** from the (+) to the (−) enantiomer was observed (Table 5, entries 2 and 3).

3. Conclusions

In summary we have developed new conditions for the synthesis of sterically hindered biaryls by Suzuki cross-coupling reactions. Di- and trisubstituted biaryls were obtained in good yield in 3–6 h reaction time. The use of cesium fluoride to effect the boron to palladium transmetallation in anhydrous solvent appears to be successful and these conditions avoid the protonolysis of the boronic acid. We have studied asymmetric Suzuki coupling with chiral phosphine ligands and the results obtained show that the ratio of BINAP and TolBINAP to $Pd(OAc)_2$ or $(\eta^3\text{-allylPdCl})_2$ influences the direction of the enantioselection.

4. Experimental

4.1. General considerations

Flash chromatography purification with silica gel was performed using Merck Kieselgel (70–230 mesh). Reactions were monitored by thin-layer chromatography carried out on silica gel coated glass plates ($60F_{254}$, Merck) ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-200 or Avance 400 instruments. IR spectra were determined on a Perkin–Elmer Spectrum One spectrophotometer. Optical rotations were measured with a Perkin–Elmer 241C spectropolarimeter. Concentrations are reported in g/100 ml of solvent. Melting

Table 5. Coupling reaction between 2-methoxy-1-naphthylboronic acid 1 and 1-iodo-2-methoxynaphthalene 2 using (*S*,*S*)-CHIRAPHOS

Entry	Pd	Ligand	Ligand/Pd	Yield (%)	Ee (%)	Rotation
1	$Pd_2(dba)_3$	(*S*,*S*)-CHIRAPHOS	1.2	54	4	(+)
2	$Pd(OAc)_2$	(*S*,*S*)-CHIRAPHOS	1.6	91	9	(−)
3	$Pd(OAc)_2$	(*S*,*S*)-CHIRAPHOS	0.95	64	4	(+)

Reaction conditions: DME, 2 equiv. boronic acid, 6 equiv. CsF, 70°C.

points (mp) are uncorrected and were recorded on a heating stage microscope Reichert. All reactions were carried out under an argon atmosphere. Solvents used for Suzuki coupling reactions were degassed before use by the 'freeze and pump' method. 1,2-Dimethoxyethane (DME) and dioxane were freshly distilled from Na/benzophenone. Toluene was distilled from Na. Ligands and palladium catalysts were purchased from Strem Chemical Company and used without further purification.

4.2. 1-Bromo-2-methoxynaphthalene

To a solution of 1-bromo-2-naphthol (10.34 g, 46.35 mmol) in 200 ml of dichloromethane were successively added a solution of NaOH (3.06 g, 76.5 mmol) in water (200 ml), aliquat 336 (1.05 g, 2.6 mmol) and dimethylsulfate (8.4 ml, 88.8 mmol). The mixture was stirred at room temperature until the 1-bromo-2-naphthol had been completely consumed as judged by thin-layer chromatography. The two phases were then separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were concentrated. The residue was dissolved in diethyl ether and washed with a 2N aqueous solution of NH_3, with a 2N aqueous solution of NaOH and with a saturated solution of NaCl. It was then dried over $MgSO_4$ and concentrated. Recrystallization of the residue from hexane gave 1-bromo-2-methoxynaphthalene as a white solid (10.30 g, 94%). Mp: 82–83°C, ^{1}H NMR (200 MHz, $CDCl_3$) $\delta=4.03$ (s, 3H, OCH_3), 7.28 (d, 1H, $^3J=8.6$ Hz, ar. *H*), 7.39–7.53 (m, 1H, ar. *H*), 7.53–7.61 (m, 1H, ar. *H*), 7.76–7.85 (m, 2H, ar. *H*), 8.23 (dd, 1H, $^3J=8.6$ Hz, $^4J=1.1$ Hz, ar. *H*); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta=57.1$ (*C*H$_3$), 105.9 (*C*-Br), 113.7 (*C*-H), 124.4 (*C*-H), 126.2 (*C*-H), 127.8 (*C*-H), 128.2 (*C*-H), 129.1 (*C*-H), 129.9 (*C*q.), 133.2 (*C*q), 153.8 (*C*q); IR (neat) $\nu=3046$(w), 2972(w), 2943(w), 2844(w), 1621(m), 1594(m), 1500(m), 1466(w), 1454(m), 1438(w), 1426(w), 1350(m), 1334(m), 1270(s), 1245(m), 1154(w), 1061(s), 1021(m), 970(m), 891(m), 801(s), 762(m), 743(m), 645(m) cm^{-1}.

4.3. 1-Iodo-2-methoxynaphthalene

To a solution of 2-methoxynaphthalene (0.743 g, 4.7 mmol) in acetonitrile (20 ml) was added *N*-iodosuccinimide (1.559 g, 6.9 mmol) and the reaction mixture was stirred at reflux for 30 h. The reaction solution was then cooled to room temperature and concentrated under reduced pressure. The residue was redissolved in diethyl ether, washed with a saturated aqueous $NaHCO_3$ solution and dried over $MgSO_4$. The solvents were evaporated under vacuum. Filtration of the residue through a plug of silica gel eluting with hexane/ethyl acetate 9.5/0.5 gave 1-iodo-2-methoxynaphthalene as a white powder (1.195 g, 89%). Mp: 88°C; ^{1}H NMR (200 MHz, $CDCl_3$) $\delta=4.03$ (s, 3H, OCH_3), 7.22 (d, 1H, $^3J=9.0$ Hz, ar. *H*), 7.34–7.42 (m, 1H, ar. *H*), 7.50 (m, 1H, ar. *H*), 7.75 (dd, 1H, $^3J=8.1$ Hz, $^4J=1.3$ Hz, ar. *H*), 7.84 (d, 1H, $^3J=9.0$ Hz, ar. *H*), 8.15 (d, 1H, $^3J=8.6$ Hz, ar. *H*); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta=57.3$ (O*C*H$_3$), 87.8 (*C*-I), 113.0 (*C*-H), 124.4 (*C*-H), 128.2 (*C*-H), 128.3 (*C*-H), 130.4 (*C*-H), 131.3 (*C*-H), 130.0 (*C*q), 135.7 (*C*q), 156.7 (*C*-O); IR (neat) $\nu=3042$(w), 3006(w), 2969(w), 2937(w), 2838(w), 1617(m), 1587(m), 1551(w), 1497(m), 1451(m), 1423(w), 1346(m), 1328(m), 1263(s), 1242(m), 1181(w), 1153(m), 1132(m), 1058(s), 1021(m), 959(w), 887(m), 801(s), 761(m), 743(s).

4.4. 2-Methoxy-1-naphthylboronic acid

Under argon, in a flame-dried vessel, a solution of 1-bromo-2-methoxynaphthalene (7.67 g, 32.36) in THF (50 ml) was added dropwise to the magnesium (0.905 g, 37.2 mmol) in THF (15 ml). The reaction mixture was stirred at room temperature for 2 h then at 50°C for 1 h. It was then cooled to −78°C and trimethylborate (11.4 ml, 101.7 mmol) was slowly added. After 2 h at −78°C, the mixture was allowed to warm to room temperature and stirred overnight. After addition of water (40 ml), THF was removed under reduced pressure. The mixture was extracted with dichloromethane, the combined organic phases were dried over $MgSO_4$, filtered and concentrated. Recrystallization from dichloromethane gave the boronic acid as a white powder (80% yield). Mp: 149–151°C; ^{1}H NMR (200 MHz, $CDCl_3$) $\delta=4.03$ (s, 3H, OCH_3), 6.18 (s, 2H, B(OH)$_2$), 7.28 (d, 1H, $^3J=9.1$ Hz, ar. *H*), 7.30–7.41 (m, 1H, ar. *H*), 7.46–7.55 (m, 1H, ar. *H*), 7.78 (d, 1H, $^3J=8.1$ Hz, ar. *H*), 7.95 (d, 1H, $^3J=8.9$ Hz, ar. *H*), 8.84 (d, 1H, $^3J=9.1$ Hz, ar. *H*); ^{13}C NMR (50 MHz, DMSO-d_6) $\delta=56.0$ (O*C*H$_3$), 113.6 (*C*-H), 121.7 (*C*-B), 123.0 (*C*-H), 125.8 (*C*-H), 127.3 (*C*-H), 127.8 (*C*-H), 128.4 (*C*q), 129.3 (*C*-H); 135.6 (*C*q), 158.5 (*C*-O); ^{11}B NMR ($CDCl_3$, 128.38 MHz) $\delta=33.4$; IR (neat) $\nu=3286$(b), 2988(w), 2933(w), 2837(w), 1620(w), 1588(w), 1571(w), 1507(w), 1463(w), 1434(w), 1389(w), 1331(m), 1279(m), 1241(s), 1149(m), 1059(s), 981(m), 897(w), 807(s), 784(m), 750(m), 693(w), 674(w).

4.5. General procedure for Suzuki coupling in toluene/ethanol/H_2O using $Pd(PPh_3)_4$ (Table 1)

Under argon, to a solution of $Pd(PPh_3)_4$ (0.07 equiv.) in toluene (32 ml/1.25 mmol of aryl halide) were successively added the indicated amounts of water (15 ml/1.25 mmol of aryl halide), Na_2CO_3 (5 equiv.), 2-methoxy-1-naphthylboronic acid (1–2.2 equiv.), ethanol (32 ml/1.25 mmol of aryl halide), aryl halide (1 equiv.). The reaction mixture was stirred at 70°C until the starting aryl halide had been completely consumed as judged by thin-layer chromatography (or for 16 h in the case of an incomplete conversion). The reaction mixture was then cooled to room temperature, the two phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over magnesium sulfate, the drying agent was filtered off and solvents were removed under reduced pressure. The crude material was purified by flash chromatography on silica gel (hexane/dichloromethane, 5/5).

4.6. General procedure for Suzuki coupling in toluene/ethanol/H_2O using $Pd(OAc)_2$+3PPh_3 (Table 1)

Under argon, to a solution of $Pd(OAc)_2$ (0.1 equiv.) in toluene (32 ml/1.25 mmol of aryl halide) were successively added the indicated amounts of water (15 ml/1.25 mmol of aryl halide), Na_2CO_3 (5 equiv.), 2-methoxy-1-naphthylboronic acid (1.5 equiv.), ethanol (32 ml/1.25 mmol of aryl halide), 1-iodo-2-methoxynaphthalene (1 equiv.) and triphenylphosphine (0.3 equiv.). The reaction mixture was stirred at 70°C until the starting aryl halide had been completely consumed as judged by thin-layer chromatography (or for 16 h in the case of an incomplete conversion). The reaction mixture was then cooled to room temperature, the two phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried with magnesium sulfate. The drying agent was filtered off and solvents were removed under reduced pressure. The crude material was purified by flash chromatography on silica gel (hexane/dichloromethane, 5/5).

4.7. General procedure for Suzuki coupling in DME/H_2O or DMF/H_2O using $Pd(OAc)_2$+3PPh_3 (Table 1)

Under argon, a vessel was charged with the indicated amounts of $Pd(OAc)_2$ (0.1 equiv.), organic solvent (DME or DMF) (1 ml/mmol of 1-iodo-2-methoxynaphthalene), water, base (Na_2CO_3 or $Ba(OH)_2$) (5 equiv.), 2-methoxy-1-naphthylboronic acid (1.9 equiv.), 1-iodo-2-methoxynaphthalene (1 equiv.) and triphenylphosphine (0.3 equiv.). The reaction mixture was stirred at 70°C until the starting aryl halide had been completely consumed as judged by thin-layer chromatography (or for 16 h in the case of an incomplete conversion). The reaction mixture was then cooled to room temperature, the two phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried with magnesium sulfate. The drying agent was filtered off and solvents were removed under reduced pressure. The crude material was purified by flash chromatography on silica gel (hexane/dichloromethane, 5/5).

4.8. General procedure for Suzuki coupling in anhydrous solvent using $Pd(OAc)_2$+3PPh_3 (Tables 1–3)

Under argon, a vessel was charged with the indicated amounts of $Pd(OAc)_2$ (0.03–0.1 equiv.), anhydrous organic solvent (DME or toluene) (1 ml/mmol of 1-iodo-2-methoxynaphthalene), base (5 equiv. K_3PO_4, or CsF, 3.15–4.6 equiv.), 2-methoxy-1-naphthylboronic acid (1.05–2 equiv.), 1-iodo-2-methoxynaphthalene (1 equiv.) and triphenylphosphine (0.09–0.3 equiv.). The reaction mixture was stirred at 70°C until the starting aryl halide had been completely consumed as judged by thin-layer chromatography (or for 16 h in the case of an incomplete conversion). The reaction mixture was then cooled to room temperature, the two phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried with magnesium sulfate. The drying agent was filtered off and solvents were removed under reduced pressure. The crude material was purified by flash chromatography on silica gel (hexane/dichloromethane, 5/5).

4.9. General procedure for asymmetric Suzuki coupling using $Pd(OAc)_2$ or (η^3-allylPdCl)$_2$ and a bidentate phosphine ligand (Tables 4 and 5)

A flame-dried vessel was charged under argon with the indicated amounts of Pd(II) and ligand and 1-iodo-2-methoxynaphthalene (1.0 equiv.). To the vessel was added the desired anhydrous solvent (12 ml/0.55 mmol of aryl iodide) and the mixture was heated at 50°C for 1 h. 2-Methoxy-1-naphthylboronic acid (2.0 equiv.) and anhydrous CsF (6.0 equiv.) were then added to the reaction solution and the mixture was stirred at 70°C for the indicated time in Tables 4 and 5 (3–12 h). After cooling to room temperature, water was added and the mixture was extracted with dichloromethane. The combined organic phases were dried with magnesium sulfate. The drying agent was filtered off and solvents were removed under reduced pressure. The crude material was purified by flash chromatography on silica gel (hexane/dichloromethane, 5/5).

4.10. General procedure for asymmetric Suzuki coupling using $Pd_2(dba)_3$ and a bidentate phosphine ligand (Tables 4 and 5)

A flame-dried vessel was charged under argon with the indicated amounts of $Pd_2(dba)_3$ and ligand. To the vessel was added anhydrous dioxane (12 ml/0.55 mmol of aryl iodide) and the mixture was heated at 50°C for 1 h. 1-Iodo-2-methoxynaphthalene (0.55 mmol, 1 equiv.), 2-methoxy-1-naphthylboronic acid (2.0 equiv.) and anhydrous CsF (6.0 equiv.) were then added to the reaction solution and the mixture was stirred at 70°C for the indicated time in Tables 4 and 5 (3–12 h). After cooling to room temperature, water was added and the mixture was extracted with dichloromethane. The com-

bined organic phases were dried with magnesium sulfate. The drying agent was filtered off and solvents were removed under reduced pressure. The crude material was purified by flash chromatography on silica gel (hexane/dichloromethane, 5/5).

4.10.1. 2,2′-Dimethoxy-1,1′-dinaphthalene. ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 3.77$ (s, 6H, OCH_3), 7.08–7.36 (m, 6H, ar. *H*), 7.46 (d, 2H, $^3J = 9.3$ Hz, ar. H), 7.87 (d, 2H, $^3J = 7.3$ Hz, ar. H), 7.98 (d, 2H, $^3J = 8.8$ Hz, ar. H); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 57.0$ (OCH_3), 114.7 (*C*-H), 120.1 (*C*q), 123.9 (*C*-H), 125.7 (*C*-H), 126.7 (*C*-H), 128.3 (*C*-H), 129.6 (*C*q), 129.8 (*C*-H), 134.4 (*C*q), 155.4 (*C*-O); IR (neat) $\nu = 3065$(w), 3010(w), 2954(w), 2934(w), 2837(w), 1618(m), 1590(m), 1505(m), 1460(m), 1354(m), 1323(w), 1263(m), 1249(s), 1149(m), 1132(m), 1090(m), 1064(m), 1019(m), 896(m), 805(s), 747(s), 708(w), 679(w).

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