CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200600616

Efficient Synthesis of Chiral 1,1′-Binaphthalenes by the Asymmetric Suzuki–Miyaura Reaction: Dramatic Synthetic Improvement by Simple Purification of Naphthylboronic Acids

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Abstract: Naphthylboronic acids prepared as reported in the literature are contaminated with HCl. A very simple purification prior to their use in Suzuki–Miyaura couplings has been found to be crucial, rendering efficient some reactions that had been reported in the literature either to fail or to give extremely poor yields. With this improvement, parent boronic acids can be used instead of esters at moderate temperatures, and bromo derivatives can be used instead of iodo derivatives. Convenient access to chiral sterically hindered binaphthalene derivatives has been achieved through the use of boronic acids, bromonaphthalenes, and ferrocenylphosphane ligands. The products were obtained in good yields (95–55%) and with good enantioselectivities (90–50%). Bulkier ligands are less efficient in the coupling of hindered partners.

Keywords: asymmetric synthesis · binaphthyls · boronic acids · enantioselectivity · Suzuki–Miyaura reaction

Introduction

The biarene subunit is a central building block in a large number of natural products. Moreover, optically active 1,1′-binaphthalene derivatives are an important class of compounds that have found extensive use as chiral auxiliaries for asymmetric syntheses.[1,2] Except in a very few cases in which chiral chromatography has been applied, optically active biphenyls and binaphthalenes are classically obtained by optical resolution of their racemates after derivatization with enantiomerically pure reagents to give diastereomers that are separated and then treated to recover the pure enantiomers.[3–6] There is much interest in the development of methods other than these cumbersome procedures, and one obvious possibility is enantioselective catalytic cross-coupling.

A pioneering work, reported in 1988 by Hayashi and Ito, involved the Kharasch coupling between (2-methylnaphthalen-1-yl)magnesium bromide and 2-methylnaphthalen-1-yl bromide to give 2,2′-dimethyl-1,1′-binaphthalene in 69% yield and up to 95% enantiomeric excess.[7] However, organomagnesium derivatives are not compatible with some functionalities that are common in natural products chemistry.[8] The Suzuki–Miyaura coupling reaction is gaining popularity over other coupling processes for a number of well known reasons, such as ease of handling of the reagents and its wider functional group tolerance. In spite of this, though, a thorough examination of the literature afforded only a very few studies of Suzuki–Miyaura couplings in enantioselective catalytic asymmetric syntheses of binaphthalenes, hindered aryls, and related systems.[9] The first, and so far best (in terms of asymmetric induction), Suzuki–Miyaura syntheses of chiral binaphthalene derivatives were reported by Cammidge and Crépy in 2000, and included—as the most hindered synthesis—that of 2,2′-dimethyl-1,1′-binaphthalene in 60% yield and up to 85% enantiomeric excess, through the use of $PdCl_2$, boronic ester as nucleophile, and 2-(diphenylphosphinoferrocenyl)ethyldimethylamine as catalyst.[10,11] Sadly, this procedure has serious drawbacks that are discussed below. In 2003, Johannsen and Jensen communicated the asymmetric synthesis of 2,2′-dimethyl-1,1′-binaphthalene by using 2-methylnaphthalen-1-ylboronic acid and a planar chiral bis(dicyclohexyl)-phosphinoferrocene/palladium complex as catalyst, in 65% yield but with only 54% enantiomeric excess.[12]

Although other related successful couplings of less hindered fragments have been reported by Yin and Buchwald (aryl-naphthyl enantioselective heterocoupling),[13] Colobert and co-workers (asymmetric synthesis of 2,2′-dimethoxy-1,1′-binaphthalene),[14] and Mikami et al. (heterocoupling of

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naphthalen-1-ylboronic acid and substituted 1-bromonaphthalenes),[15] it is clear that achieving satisfactory yields when both coupling partners bear substituents at the α position to the halogen and the boron atom (particularly the construction of 2,2′-dimethyl-1,1′-binaphthalene, which represents an extreme case) is a very difficult task. In fact, a close examination of the reaction conditions for the best procedure available to date for the preparation of 2,2′-dimethyl-1,1′-binaphthalene shows that the reported synthesis requires long reaction times (6–9 days), addition of 3% chiral catalyst every 24 h (which amounts to 18–27% catalyst for the complete process), and the need to prepare boronate esters and iodonaphthalenes (bromonaphthalenes are commercially available but iodonaphthalenes are not) as the reagents.[10,11] A more convenient synthetic procedure for the enantioselective Suzuki coupling of extended, sterically demanding aromatic systems (such as substituted 1-halonaphthalenes and 1-substituted naphthylboronic compounds) would be desirable, and the synthesis of the challenging 2,2′-dimethyl-1,1′-binaphthalene is a good touchstone for such modified procedures. Hopefully some of the improvements in the Suzuki method achieved for challenging products may also be useful for the coupling of a wider range of sterically congested partners, important in asymmetric natural products synthesis, and even for routine couplings.

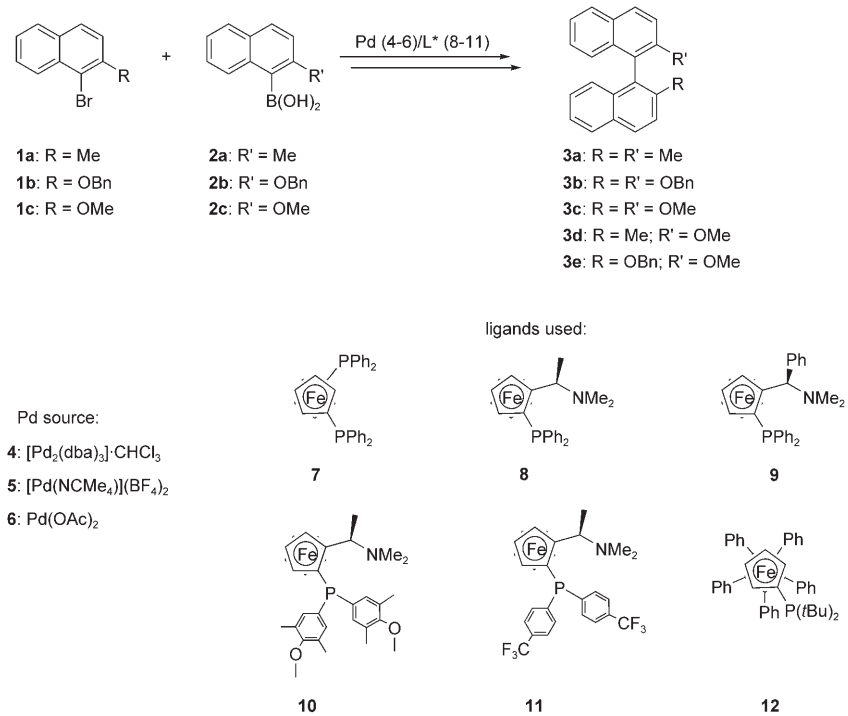
We decided to approach the problem by refining Cammidge's method, and during this process of refinement we uncovered a problem associated with the use of boronic acids that seems to have gone unnoticed and seriously affects their performance. We cannot know the real extent of the problem,[16] but one can wonder whether this may have been the cause for them being replaced by more sophisticated and expensive reagents. Here we report the solution to this problem, which allows an efficient use of boronic acid reagents and gives a very much improved method for the synthesis of chiral binaphthalene derivatives.

Results and Discussion

The coupling reagents (**1a–c** and **2a–c**) were selected as representative of steric demand (Scheme 1). With this choice we were already including the improvement and additional challenge of using the less reactive bromides **1a–c**, which are either commercially available (**1a**) or have commercially available and cheap immediate naphthol precursors (**1b–c**), rather than more reactive corresponding iodides, which are not commercially available and require elaborate syntheses through lithiation, quenching with iodine, and chromatography. Unlike that of **3a**, the other syntheses (of **3b** and **3c**) in satisfactory yields have not been reported so far in enantioselective variants.

The commercially unavailable naphthyl bromides **1b** and **1c** were synthesized by literature procedures, by etherification of 1-bromo-2-naphthol with the corresponding methyl or benzyl halide.[17] The boronic acids (**2a–c**) were obtained from the corresponding lithium or Grignard reagents by quenching with trimethyl borate and acidic hydrolysis.[11,14,17,18] The commercially available achiral ligand 1,1′-bis(diphenylphosphino)ferrocene (dppf; **7**) was found to be very efficient for these couplings. The achiral ligand **12**,[19] which is impressively active in the coupling of a wide range of aryl–aryl Suzuki couplings, was also checked, but it turned out to be inefficient in these couplings. As chiral ligands we examined the ferrocenyl monophosphane derivative (R,S_p)-[1-(2-diphenylphosphino-ferrocenyl)ethyl]-dimethylamine ((R,S_p)-(−)-PFNMe, **8**), which is easily available by standard methods from the commercially available (*R*)-(+)-(1-ferrocenylethyl)-dimethylamine,[20] as well as three other (R,S_p)-chiral ferrocenylmonophosphanes (**9–11**). Prior to optimization of the enantioselectivity tests, some studies were carried out in order to solve problems of reactivity encountered in the early stages of this study (Table 1).

Purification of boronic acids: A big problem in Suzuki syntheses using boronic acid derivatives $RB(OH)_2$ is extensive



Scheme 1.

Table 1. Results from the racemic Suzuki–Miyaura couplings.[a]

Entry	Halide	Boronic acid **2** (purification)	Product	Pd source (mol% Pd)	Ligand (mol%)	T [°C]	t [h]	Yield[b] [%]
1	**1a**	**2a** (no)	**3a**	$PdCl_2$ (3)	**8** (6)	85	35	n.o.
2	**1a**	**2a** (yes)	**3a**	$PdCl_2$ (3)	**8** (6)	85	96	20
3	**1a**	**2a** (yes)	**3a**	$PdCl_2$ (3)	**8** (6)	85	144	58[c]
4	**1a**	**2a** (no)	**3a**	$PdCl_2$ (3)	**7** (3)	85	96	n.o.
5	**1a**	**2a** (yes)	**3a**	$PdCl_2$ (3)	**7** (3)	85	96	20
6	**1a**	**2a** (yes)	**3a**	$PdCl_2$ (10)	**7** (12)	85	96	20
7	**1a**	**2a** (yes)	**3a**	$[Pd_2(dba)_3]$ (10)	**7** (12)	60	72	95
8	**1b**	**2b** (no)	**3b**	$PdCl_2$ (10)	**7** (12)	85	96	traces
9	**1b**	**2b** (yes)	**3b**	$PdCl_2$ (10)	**7** (12)	50	72	95
10	**1a**	**2a** (yes)	**3a**	$[Pd_2(dba)_3]$ (10)	**12** (20)	60	96	25
11	**13**	**2a** (yes)	**15**	$[Pd_2(dba)_3]$ (10)	**7** (12)	65	48	85
12	**14**	**2a** (yes)	**16**	$[Pd_2(dba)_3]$ (10)	**7** (12)	65	72	68

[a] CsF was used as base in all reactions; reactants ratio: bromide (**1**)/boronic acid (**2**)/CsF 1:1.8:3; solvents used (12.5 mL per 1 mmol of **1**): THF for entries 7 and 10–12, DME for all other entries. [b] Isolated yield after chromatography. [c] Addition of catalyst every 24 h.

deboronation, giving rise to RH. This problem is particularly serious when sterically hindered partners are involved and the coupling becomes more difficult,[11,21] but is not exclusive to these systems. Indeed it is a well known ubiquitous problem not explicitly mentioned in papers but implicit in the high boronic acid derivative/organic electrophile ratios used in the reactions (5:1 ratios are common in the literature). Boronate cyclic esters are often preferred, in spite of the fact that they require one more synthetic step, because the degree of deboronation encountered with these reagents is lower.

The naphthylboronic acids obtained by literature procedures,[17,18] and referred to as "crude" in this paper, were completely inactive in our coupling reactions between sterically hindered partners, and we found that they retained noticeable amounts of HCl, which is used in the last step of their preparation. With the crude products, extensive deboronation was observed within a couple of hours, causing the failure of the attempted syntheses. The HCl contaminating the naphthylboronic acids is retained fairly strongly (probably because of hydrogen bonding to the OH groups of the boronic acids) and is not eliminated by subjection of the boronic acids to vacuum overnight (after this treatment the boronic acid/HCl ratio was still 6.8:1). Recrystallization from pentane/chloroform was only partially effective, while washing with water until neutral pH was much more effective, but came at the expense of losing some boronic acid, which is partially soluble in water. The best method we found to remove HCl completely (as well as some minor organic contaminants) was simple flash chromatography filtration (silica) of the crude boronic acids. The products obtained upon evaporation showed neutral pH values, and dramatic improvements in the yields of the reactions were observed. In fact, the purification of the boronic acids by flash chromatography provided yields comparable to those reported for boronic ethers in model reactions.

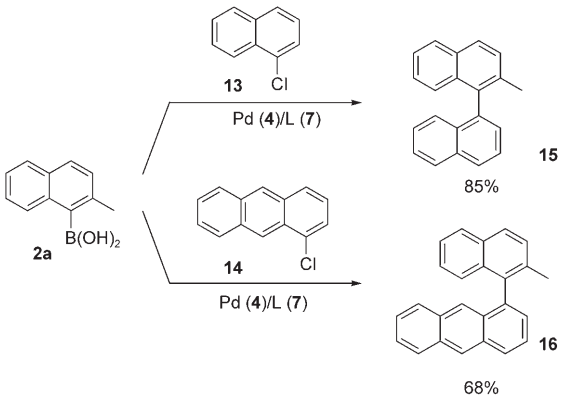
A few experiments, collected in Table 1, are worth commenting on in this respect. Comparison of entries 1–3, which are similar to the attempted synthesis of **3a** reported by Cammidge (but use the bromo derivative of the naphthyl electrophile instead of the iodo derivative), shows that the reaction does not take place with the crude boronic acid. This is consistent with the results reported for the attempted synthesis of **3a** by Cammidge, who found that "no product was obtained when the parent boronic acid was employed (using the above optimal conditions) and complete deboronation was observed". The same reaction gave a 20% yield after 96 h when our purification procedure was used and 58% in 144 h (we did not try for longer) when, in addition, Cammidge's technique of adding 3% of Pd catalyst every 24 h was applied. The increase in yield observed in entry 3 relative to entry 2 shows that, when purified, the boronic acid has not been fully degraded after 96 h, as happens in entry 1, and it is only the loss of Pd catalyst by decomposition that needs to be rectified.

Entries 4 and 5, with dppf as ligand, again show that the reaction does not succeed with crude boronic acid but does work under similar conditions with purified boronic acid. Moreover, the yields were similar for the reaction in the presence of 3 mol% of bidentate dppf (entry 5) and that in the presence of 6 mol% of monodentate **8** (entry 2). For this reason all the experiments intended to check or optimize chemical yields were carried out with the commercial dppf before being modified to their enantioselective versions with **8**. An increase in the amount of $PdCl_2$ from 3 to 10% (entries 5 and 6) did not produce any crucial change, but changing the precatalyst to $[Pd_2(dba)_3]$ increased the yield to 95% (entry 7). This prompted us to examine different catalysts, and only the best results obtained are given below for the chiral version.

For the less challenging coupling between **1b** and **2b** the effect of using flash chromatographically purified boronic acid was enormous, the yield of the reaction changing from traces (entry 8) to 95% (entry 9). This indicates that the use of carefully purified boronic acids is crucial for the success of the syntheses, rendering the use of boronic ethers unnecessary.

In order to illustrate the generality of our procedure we performed the coupling between the most sterically demanding boronic acid **2a** and the commercially available 1-chloronaphthalene (**13**) and 1-chloroanthracene (Scheme 2). The products **15** and **16** were obtained in yields of 85 and 68%, respectively (Table 1, entries 11 and 12), which are very good in view of the challenging fragments to be coupled. To the best of our knowledge this is the first example of coupling of the poorly reactive 1-chloroanthracene.

Enantioselective couplings: Suzuki couplings to give racemic **3a–c** (Scheme 1), in the presence of dppf (**7**) as ligand, were



Scheme 2.

carried out in order to identify optimal reaction conditions for high yields, and some smaller-scale variations with use of the corresponding chiral ligand were then made to find a good compromise between yield and enantioselectivity. Table 2 collects the best reaction conditions found, along with other results relevant to the discussion. The reactions were carried out under anhydrous conditions, the most suitable solvents found being DME (dimethoxyethane) and THF, other solvents or mixtures (toluene/ethanol/water,[22] DME/water) not giving satisfactory results. Of all bases tested, CsF gave the best results, consistently with the experiments reported by Cammidge. Our alternative tests using $Ba(OH)_2$, K_3PO_4, KF, Na_2CO_3, NaOH, or even Cs_2CO_3 (anhydrous and aqueous conditions) afforded only traces of the products.

It is noticeable that the reactions work perfectly with a moderate boronic acid/naphthyl bromide ratio (1.8:1), due to the fact that the rate of deboronation is markedly reduced when purified boronic acids are used.

The palladium source had a marked influence on the reactions, and other palladium compounds afforded much better results than $PdCl_2$ (cf. entries 2, 3, 5 and 6 in Table 1 and entries 1–3 and 6 in Table 2). The Pd^0 complex $[Pd_2(dba)_3]$ (**4**) or the Pd^{II} compounds $[Pd(NCMe)_4](BF_4)_2$ (**5**) and $Pd(OAc)_2$ (**6**) are recommended in Table 2, depending on the yields achieved in each case.

In general, all the reactions proceeded in very high yields when 10 mol% Pd were used. It is important to note that under these conditions the reactions could be carried out at moderate temperatures (not above 65 °C), whereas the usual conditions in the literature involve heating at reflux in mixed solutions. For comparison, it is interesting to note that efficient couplings of hindered fragments in the literature have been reported to demand 20–40% of Pd catalyst.[23]

Although a severe reduction in Pd source resulted in failure of the reaction, the amount of catalyst could sometimes be reduced noticeably without much loss of yield. A reduction in the Pd loading to 5 mol% with maintenance of the same amount of ligand did not affect the yield of **3a** (Table 2, entry 2 vs entry 1), while the use of tetrakisacetonitrile palladium(II) tetrafluoroborate (**5**)[15] (3 mol%) with 12 mol% of the chiral ligand **7** gave a moderate increase in enantioselectivity, from 85% to 90% in the case of **3a**, but a decrease in the yield to 55% (Table 2, entry 3). Reducing the Pd loading from 10 to 5 mol% and keeping the same amount of ligand decreased the yields of **3b** and **3c** while increasing the enantioselectivities of both reactions (Table 2, entries 5 and 7 vs entries 4 and 6, respectively). Although the source of catalyst in these experiments is different, the results seem to support the notion that, for a given coupling, a decrease in yield is associated with an increase in selectivity, as also observed in entries 1–3 for **3a**. Of all the ligands used, the best results were achieved with **8**. Decreases in yield and enantioselectivity were observed as steric hindrance of the ligands (**9**–**11**) increased (Table 2, entries 8–16). This result was somewhat unexpected (ligands **9**–**11** often provide better enantioselectivity in the reactions in which they participate) and suggests that less bulky ligands are better able to recognize and discriminate between bulky reagents. This is clearly illustrated with the use of the Hartwig's di-*tert*-butylphosphinoferrocene ligand **12** (Scheme 1), which showed only

Table 2. Results from the optimized asymmetric Suzuki couplings.[a]

Entry	Bromide **1**	Boronic acid **2**	Product **3**	Pd source (mol% Pd)	Ligand [mol%]	T [°C]	t [h]	Yield[b] [%]	ee[c] [%] (conf.)
1	**1a**	**2a**	**3a**	**4** (10)	**8** (20)	65	72	85	85 (*S*)
2	**1a**	**2a**	**3a**	**4** (5)	**8** (20)	65	72	85	85 (*S*)
3	**1a**	**2a**	**3a**	**5** (3)	**8** (12)	65	96	55	90 (*S*)
4	**1b**	**2b**	**3b**	**6** (10)	**8** (20)	50	72	95	60 (*S*)
5	**1b**	**2b**	**3b**	**4** (5)	**8** (20)	65	96	50	88 (*S*)
6	**1c**	**2c**	**3c**	**6** (10)	**8** (20)	50	72	95	50 (*S*)
7	**1c**	**2c**	**3c**	**4** (5)	**8** (20)	65	96	50	57 (*S*)
8	**1a**	**2a**	**3a**	**4** (10)	**9** (20)	65	72	62	73 (*S*)
9	**1b**	**2b**	**3b**	**6** (10)	**9** (20)	50	96	86	37 (*S*)
10	**1a**	**2a**	**3a**	**4** (10)	**10** (20)	65	72	50	68 (*S*)
11	**1b**	**2b**	**3b**	**6** (10)	**10** (20)	50	72	45	66 (*S*)
15	**1a**	**2a**	**3a**	**4** (10)	**11** (20)	65	72	66	68 (*S*)
16	**1b**	**2b**	**3b**	**6** (10)	**11** (20)	50	72	75	33 (*S*)
17	**1a**	**2c**	**3d**	**4** (5)	**8** (20)	65	96	80	73 (n/a)
18	**1c**	**2a**	**3d**	**4** (5)	**8** (20)	65	96	77	65 (n/a)
19	**1b**	**2c**	**3e**	**4** (5)	**8** (20)	65	48	93	62 (n/a)
20	**1c**	**2b**	**3e**	**4** (5)	**8** (20)	65	48	90	60 (n/a)

[a] CsF was used as base in all reactions; reactants ratio: bromide (**1**)/boronic acid (**2**)/CsF = 1:1.8:3; solvents used (12.5 mL per 1 mmol of **1**): THF for entries 1, 4–6, 8, 11, 13, 15, and 17–20, DME for all other entries. [b] Isolated yield after chromatography, deboronation product was always present. [c] Determined by optical rotation and/or HPLC measurements.

moderate efficiency in the synthesis of **3a** (Table 1, entry 10).

Several mixed couplings with ligand **8** were also performed (Table 1, entries 17–20). In all cases the reactions proceeded with excellent yields and good to moderate enantioselectivities. Interestingly, the enantioselectivity of the reaction affording **3d** from **1a** and **2c** was higher than that starting from **1c** and **2a**, while the yield remained unaffected (Table 2, entry 17 vs 18). In the case of **3e** both reactions (**1b+2c** and **1c+2b**) proceeded with similar yields and enantioselectivities (Table 2, entries 19 and 20).

Conclusion

Naphthylboronic acids retain noticeable amounts of HCl, used in the last step of their preparation. Since such HCl addition is frequently the last step in the preparation of boronic acids, the problem found for the naphthylboronic acids is a warning that careful checking and purification may also be needed in other cases.

A very simple flash chromatographic filtration of the naphthylboronic acids prior to their use in Suzuki–Miyaura couplings dramatically reduces the deboronation problem associated with them, improving their efficiency as reagents and enabling their use even in demanding reactions.

This is shown in the challenging cases of: i) the enantioselective preparation of sterically hindered 2,2′-substituted binaphthalenes, which was achieved with the use of boronic acids (no need to prepare their boronic esters), naphthyl bromides (no need to use iodides), a moderate boronic acid/naphthyl bromide ratio (1.8:1), moderate temperatures, and a reasonable amount of catalyst (5–10%), and ii) the preparation of sterically hindered naphthyl-substituted anthracene, achieved from anthracen-1-yl chloride. It is interesting to note that the reported reactions can be scaled up to multigram preparations without any reduction in yield or enantioselectivity. Moreover, studies underway in our laboratory suggest that the same reaction procedure and similar conditions can successfully be applied to the enantioselective synthesis of a wide range of other sterically demanding fragments.

Experimental Section

General information: All reactions were carried out under argon. Diethyl ether, THF, and DME were dried over Na/benzophenone and distilled. Acetonitrile was dried over CaH_2 and distilled. Flash chromatography was performed on silica gel (silica gel 60, 230–400 mesh, Merck). Deactivated silica gel was prepared by treatment with Et_3N in pentane (10%) and drying in vacuo. TLC was performed with Macherey–Nagel 60 F_{254} precoated silica gel plates. All NMR experiments were performed on Bruker ARX 300 and AC 300 spectrometers. Optical rotations were measured on a Perkin–Elmer 343 instrument. Analytical HPLC was carried out by using Shimadzu and Waters HPLC systems with Daicel Chiralpak AD and Chiralcel OJ-R columns, with use of heptane/propan-2-ol and methanol/water, respectively, as eluting solvents. Elemental analyses were performed on a Perkin–Elmer 2400 CHN elemental analyzer. Melting points are uncorrected. Mass spectra were obtained on a Agilent Technology 5973 INERT machine. 1-Bromo-2-methylnaphthalene (**1a**, 95%), 1-bromo-2-naphthol (97%), 1-chloronaphthalene (95%), 1-chloroanthracene (97%), and (*R*)-(+)-(1-ferrocenylethyl)dimethylamine (>98%) are commercially available. The starting materials **1b**,[17] **1c**,[17] **8**,[20] and **12**[19] were synthesized by literature procedures with very small modifications. The boronic acids **2a–c** were prepared by literature methods, but purity is a critical factor for the success of the coupling reactions, and for this reason their preparations are reported here in detail. The spectral data for the coupling products **3a–c** obtained by our procedure are completely coincident with those reported in the literature. Our synthetic method is reported in detail, and the references for the previous reports on all these compounds are given.

2-Methylnaphthalen-1-ylboronic acid (2a):[11,18] A solution of 1-bromo-2-methylnaphthalene (8.60 g, 38.80 mmol) in anhydrous THF (25 mL) was added to freshly activated magnesium turnings (1.04 g, 42.7 mmol). The mixture was stirred under reflux for 3 h. Trimethyl borate (4.48 g, 42.70 mmol) was added slowly at 0 °C, the mixture was stirred at room temperature for 4 h, and aqueous hydrochloric acid (1 M, 12 mL) was added slowly to give a gray precipitate. The mixture was stirred overnight at room temperature and was then diluted with dichloromethane (100 mL) and washed with distilled water (3×50 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated in vacuum to give a yellow oil, which was dissolved in pentane (20 mL), and concentrated aqueous hydrochloric acid (1 mL) was added. The mixture was stirred at room temperature for 4 h, during which time a white precipitate was formed. The precipitate was filtered, loaded onto a column (15×10 cm), and eluted first with hexanes/diethyl ether 3:1 in order to remove the 2-methylnaphthalene and then with hexanes/diethyl ether 1:2 to give the title compound as a white solid (4.08 g, 57%). M.p. 126 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.59 (s, 3H), 4.95 (s, 2H), 7.32 (d, J = 8.2 Hz, 1H), 7.42–7.48 (m, 2H), 7.76–7.87 ppm (m, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 22.4, 125.0, 126.3, 127.4, 128.3 (2C), 128.9, 131.3, 135.1, 138.2 ppm; elemental analysis (%) calcd for $C_{11}H_{11}BO_2$: C 71.03, H 5.96; found: C 71.10, H 6.09.

2-Benzyloxynaphthalen-1-ylboronic acid (2b):[17] *n*-Butyllithium (15.8 mL, 1.6 M in hexanes) was added at −70 °C to a suspension of 2-benzyloxy-1-bromonapthalene (**1b**, 7.92 g, 25.30 mmol) in diethyl ether (90 mL) and the mixture was stirred at 0 °C for 1.5 h. After having been recooled to −70 °C, the mixture was treated with trimethyl borate (3.13 mL, 27.8 mmol) and allowed to warm to room temperature overnight. The resulting mixture was quenched with aqueous hydrochloric acid (1 M, 60 mL), stirred at room temperature for 1.5 h, extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated to give a yellow oil. This oil was dissolved in pentane (20 mL), concentrated aqueous hydrochloric acid (1 mL) was added, and the mixture was stirred at room temperature for 4 h, during which a white precipitate was formed. The precipitate was filtered, loaded onto a column (15×10 cm), and eluted first with hexanes/diethyl ether 5:1 in order to remove 2-benzyloxynaphthalene and then with hexanes/diethyl ether 2:1 to give the title compound **2b** as a white solid (4.92 g, 70%). M.p. 134–136 °C; ^{1}H NMR (300.13 MHz, CD_3OD): δ = 4.90 (s, 2H), 5.25 (s, 2H), 7.33–7.60 (m, 9H), 7.56–7.88 ppm (m, 2H); ^{13}C NMR (75.47 MHz, CD_3OD): δ = 72.0, 118.0, 122.5, 125.0 (2C), 126.4, 127.6 (2C), 131.8, 137.2, 139.0, 160.0 ppm; elemental analysis (%) calcd for $C_{17}H_{15}BO_3$: C 73.42, H 5.44; found: C 73.49, H 5.40.

2-Methoxynaphthalen-1-ylboronic acid (2c):[14] *n*-Butyllithium (18.60 mL, 1.6 M in hexanes) was added at −70 °C to a suspension of 1-bromo-2-methoxynapthalene (**1c**, 7.00 g, 29.52 mmol) in diethyl ether (90 mL) and the mixture was stirred at 0 °C for 1.5 h. After having been cooled to −70 °C, the mixture was treated with trimethyl borate (3.66 mL, 32.48 mmol) and allowed to warm to room temperature overnight. The resulting mixture was quenched with aqueous hydrochloric acid (1 M, 70 mL), stirred at room temperature for 1.5 h, extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated to give a yellow oil. This oil was dissolved in pentane (20 mL), concentrated aqueous hydrochloric acid (1 mL) was added, and the mixture was stirred at room temperature for 4 h, during which a white precipitate was formed. The precipitate was filtered, loaded on a column (15×10 cm), and eluted first with hexanes/di-

ethyl ether 4:1 in order to remove the 2-methoxynaphthalene and then with hexanes/diethyl ether 1:1 to give the title compound as a white solid (4.29 g, 71%). M.p. 150°C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 4.08 (s, 3H), 6.22 (s, 2H), 7.28 (d, J = 9.1 Hz, 1H), 7.34–7.43 (m, 1H), 7.47–7.56 (m, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.98 (d, J = 8.9 Hz, 1H), 8.86 ppm (d, J = 9.1 Hz, 1H); ^{13}C NMR (75.47 MHz, [D$_6$]DMSO): δ = 56.1, 113.7, 121.8, 122.7, 125.8, 127.4, 127.8, 128.5, 129.4, 135.6, 159.0 ppm; elemental analysis (%) calcd for $C_{11}H_{11}BO_3$: C 65.40, H 5.49; found: C 64.90, H 5.47.

General procedure for the Suzuki coupling reactions: The desired bromide (**1a–c**, 0.16 mmol), the palladium source (**4–6**, 0.016 or 0.008 mmol Pd), the chiral ligand **8–11** (0.032 mmol), the corresponding boronic acid (**2a–c**, 0.29 mmol), and CsF (0.50 mmol) were introduced into a dry 50 mL Schlenk flask fitted with a Young's tap and containing a Teflon stirring bar. Anhydrous THF or DME (2 mL) was added, the flask was sealed, and the mixture was stirred and heated at the indicated temperature. The progress of the reaction was monitored by TLC. After the time specified in Table 2, the reaction mixture was treated with distilled water (10 mL), extracted with CH_2Cl_2 (3×10 mL), dried ($MgSO_4$), and purified by flash chromatography (hexanes for **3a** and hexanes/diethyl ether 7:1 for **3b** and **3c**) to give the corresponding product (**3a–c**).

2,2′-Dimethyl-1,1′-binaphthalene (3a): Colorless oil, R_f = 0.45 (hexanes); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.08 (s, 6H), 7.10 (d, J = 8.3 Hz, 2H), 7.25 (m, 2H), 7.43 (m, 2H), 7.52 (d, J = 8.3 Hz, 2H), 7.81 ppm (dd, J = 7.4 Hz, 4H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 20.2, 125.0, 125.8, 126.2, 127.6, 128.1, 128.9, 132.3, 132.9, 134.4, 135.1 ppm; elemental analysis (%) calcd for $C_{22}H_{18}$: C 93.57, H 6.43; found: C 93.64, H 6.49.

The optical purity was determined by optical rotation and comparison with that reported for the optically pure enantiomer for (*R*)-**3a** $[\alpha]_D^{22}$ = −35.6 (c = 1.0, $CHCl_3$) or $[\alpha]_D^{22}$ = −19.0 (c = 1.3, ethanol).[11] Found optical rotations: $[\alpha]_D^{22}$ = +16.2 (c = 1.29, ethanol) for 85% *ee*; $[\alpha]_D^{22}$ = +17.3 (c = 1.32, ethanol) for 90% *ee* (Table 2, entry 3). In this case HPLC determination was impossible as perfect enantiomer separation could not be achieved.

2,2′-Bis(benzyloxy)-1,1′-binaphthalene (3b): Thick, yellowish oil; R_f = 0.30 (hexanes/diethyl ether 7:1); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 5.10 (s, 4H), 7.05 (d, J = 6.5 Hz, 4H), 7.09–7.21 (m, 6H), 7.28 (d, J = 6.5 Hz, 4H), 7.36–7.44 (m, 2H), 7.48 (d, J = 9.0 Hz, 2H), 7.90–8.10 ppm (m, 4H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 71.1, 116.0, 120.7, 123.7, 125.6, 126.3, 126.7, 127.3 127.9, 128.1, 129.3, 129.4, 134.2, 137.6, 154.1 ppm; elemental analysis (%) calcd for $C_{34}H_{26}O_2$: C 87.52, H 5.62; found: C 87.58, H 5.69.

The optical purity of our product **3b** was determined by HPLC and optical rotation measurements: Daicel Chiralpak AD 0.46 cm×25 cm, heptane/isopropanol 98:2, 20°C, flow rate 0.5 mL min^{-1}, UV detection at 220 or 254 nm; (*S*)-(−)-**3b**: t_r = 24.3 min; (*R*)-(+)-**3b**: t_r = 34.0 min. Optical rotation for optically pure (*S*)-(−)-**3b** $[\alpha]_D^{20}$ = −45.5 (c = 0.5, CH_2Cl_2).[24] Optical rotation found: $[\alpha]_D^{22}$ = −27.5 (c = 0.52, CH_2Cl_2) for 60% *ee*; $[\alpha]_D^{22}$ = −40.0 (c = 0.48, CH_2Cl_2) for 88% *ee* (Table 2, entry 5).

2,2′-Dimethoxy-1,1′-binaphthalene (3c): White crystals; R_f = 0.25 (hexanes/diethyl ether 7:1); m.p. 197–204°C (decomp.); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.75 (s, 6H), 7.06–7.34 (m, 6H), 7.45 (d, J = 9.2 Hz, 2H), 7.86 (d, J = 7.2 Hz, 2H), 7.98 ppm (d, J = 8.5 Hz, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 56.8, 114.2, 119.5, 123.5, 125.2, 126.3, 127.9, 129.2, 129.4, 134.0, 154.9 ppm; elemental analysis (%) calcd for $C_{22}H_{18}O_2$: C 84.05, H 5.77; found: C 84.09, H 5.83.

The optical purity of our product **3c** was determined by HPLC and optical rotation measurements: Daicel Chiralpak AD 0.46 cm×25 cm, heptane/isopropanol 98:2, 20°C, flow rate 0.5 mL min^{-1}, UV detection at 220 nm; (*S*)-(−)-**3c**: t_r = 34.5 min; (*R*)-(+)-**3c**: t_r = 42.0 min. Optical rotation for (*S*)-(−)-**3c** $[\alpha]_D^{20}$ = −54 (c = 1.0, $CHCl_3$).[25] Optical rotation found for our product: $[\alpha]_D^{22}$ = −27.2 (c = 1.03, $CHCl_3$) for 50% *ee* (Table 2, entry 6); $[\alpha]_D^{22}$ = −31.0 (c = 0.99, $CHCl_3$) for 57% *ee* (Table 2, entry 7).

2-Methoxy-2′-methyl-1,1′-binaphthalene (3d): Thick, colorless oil; R_f = 0.45 (hexanes/diethyl ether 20:1); $[\alpha]_D^{22}$ = +9.3 (c = 0.45, $CHCl_3$) for 72% *ee*; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.11 (s, 3H), 3.78 (s, 3H), 7.01 (d, J = 9.0 Hz, 1H), 7.14 (d, J = 8.1 Hz, 1H), 7.19–7.25 (m, 2H), 7.30–7.42 (m, 3H), 7.46–7.54 (m, 2H), 7.89 (d, J = 8.1 Hz, 1H), 8.00 ppm (d, J = 9.0 Hz, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 20.3, 56.5, 113.7, 121.8, 123.5, 124.7, 125.0, 125.8, 125.8, 126.5, 127.5, 127.9, 127.9, 128.6, 129.1, 129.3, 132.0, 132.3, 133.1, 133.6, 134.9, 154.3 ppm; MS (EI): m/z (%): 298 (100) $[M]^+$, 283 (10), 268 (36), 252 (14), 239 (16), 226 (5), 134 (12), 120 (10) ppm; elemental analysis (%) calcd for $C_{22}H_{18}O$: C 88.56, H 6.08; found: C 88.60, H 6.11.

The optical purity of our product **3d** was determined by HPLC measurements: Chiralcel OJ-R 0.46 cm×15 cm, acetonitrile/water 50:50, 20°C, flow rate 0.5 mL min^{-1}, UV detection at 220 nm; (−)-**3d**: t_r = 51.17 min; (+)-**3d**: t_r = 53.86 min.

2-Benzyloxy-2′-methoxy-1,1′-binaphthalene (3e): Thick, colorless oil; R_f = 0.48 (hexanes/diethyl ether 20:1); $[\alpha]_D^{22}$ = −33.5 (c = 0.86, $CHCl_3$) for 60% *ee*; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.87 (s, 3H), 5.18 (d, J = 2.4 Hz, 2H), 7.09–7.12 (m, 2H), 7.24–7.28 (m, 4H), 7.31–7.37 (m, 3H), 7.41–7.47 (m, 2H), 7.52–7.59 (m, 2H), 7.96–8.04 (m, 3H), 8.12 ppm (d, J = 9.0 Hz, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 14.1, 22.7, 31.6, 56.6, 71.1, 113.8, 116.1, 119.3, 120.7, 123.4, 123.7, 125.4, 125.4, 126.3, 126.3, 126.7, 127.3, 127.9, 127.9, 128.1, 154.0, 154.9 ppm; MS (EI): m/z (%): 390 (77) $[M]^+$, 299 (25), 284 (6), 268 (100), 255 (10), 239 (22), 226 (12), 91 (28) ppm; elemental analysis (%) calcd for $C_{22}H_{22}O_2$: C 86.13, H 5.68; found: C 86.17, H 5.61.

The optical purity of **3e** was determined by HPLC measurements: Chiralcel OJ-R 0.46 cm×15 cm, methanol/water 90:10, 20°C, flow rate 0.5 mL min^{-1}, UV detection at 220 nm; (+)-**3e**: t_r = 29.66 min; (+)-**3e**: t_r = 37.01 min.

2-Methyl-1,1′-binaphthalene (15): White crystals, m.p. 85°C; R_f = 0.50 (hexanes); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.14 (s, 3H), 7.12–7.66 (m, 8H), 7.60 (dd, J = 7.0, 1.4 Hz, 1H), 7.87 (d, J = 8.5 Hz, 2H), 7.97 ppm (d, J = 8.5 Hz, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 20.3, 125.0, 125.7, 125.9, 126.0, 126.1, 126.2, 126.3, 127.6, 127.7, 127.8, 127.8, 128.3, 128.7, 132.1, 132.7, 133.6, 133.8, 134.5, 136.2, 137.6 ppm; elemental analysis (%) calcd for $C_{25}H_{18}$: C 93.99, H 6.01; found: C 94.08, H 5.98.

1-(2-Methylnaphthalen-1-yl)anthracene (16): White crystals, m.p. 131°C; R_f = 0.35 (hexanes); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.15 (s, 3H), 7.19–7.21 (m, 2H), 7.30–7.46 (m, 4H), 7.54–7.68 (m, 3H), 7.80 (s, 1H), 8.02 (d, J = 8.6 Hz, 1H), 8.13 ppm (d, J = 8.6 Hz, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 20.5, 124.8, 124.8, 125.2, 125.2, 125.5, 125.9, 126.3, 126.7, 127.2, 127.6, 127.7, 127.9, 127.9, 128.5, 128.7, 131.1, 131.6, 131.7, 132.0, 132.0, 133.5, 134.6, 136.1, 137.6 ppm; MS (EI): m/z (%): 318 (100) $[M]^+$, 303 (47), 151 (27) ppm; elemental analysis (%) calcd for $C_{25}H_{18}$: C 94.30, H 5.70; found: C 94.37, H 5.64.

Acknowledgements

This work was supported by the Dirección General de Investigación (MEC, Grant no. CTQ2004-07667) and the Junta de Castilla y León (Projects VA057/03 and VA058/03) and by a Marie Curie fellowship to M.G. (HPMD-CT-2000-00058). We thank Dr. Alfred Deege (Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr, Germany) and Dr. Thomas Belser (University of Basel, Switzerland) for HPLC analysis. We also thank Solvias AG for providing samples of the chiral ligands **9–11**.

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Received: May 2, 2006
Published online: September 27, 2006

