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Synthesis of chiral binaphthalenes using the asymmetric Suzuki reaction

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Abstract—The synthesis of atropisomeric 1,1′-binaphthalenes can be achieved using an asymmetric Suzuki cross-coupling reaction. The Suzuki reaction leading to such hindered compounds is challenging and competing hydrolytic deboronation frequently dominates unless carefully chosen conditions are employed. The simple, standard mechanism is inadequate when describing the Suzuki coupling of hindered partners. Evidence suggests that the key step leading to asymmetry is transmetallation (delivery of the organometallic by the asymmetric ligand) and the reactions operate under kinetic control. Reductive elimination (itself likely to be triggered by oxidative addition of another molecule of halide) is fast compared with equilibration (epimerisation and/or *cis–trans* isomerisation).
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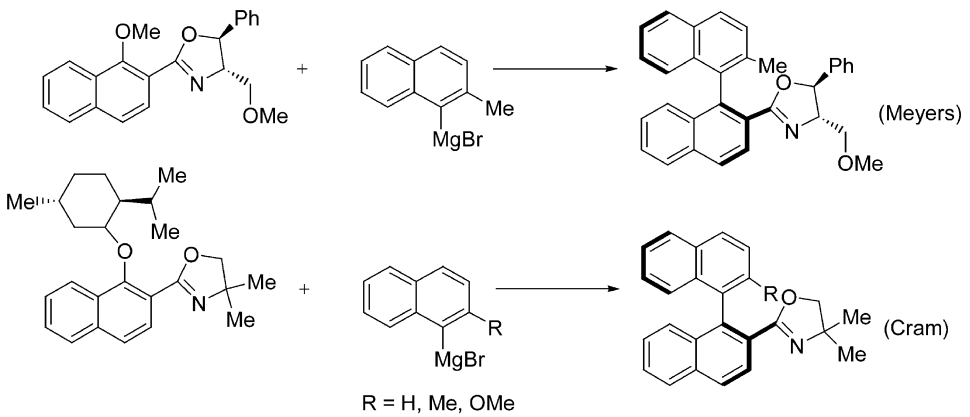
1. Introduction

Chiral binaphthalenes are an important and extensively studied class of atropisomeric compounds. The parent compound, 1,1′-binaphthalene, has received attention because early observations indicated that the racemic material spontaneously resolves into higher melting crystals containing single enantiomer molecules.[1] The resolved material racemises with a half life of 14.5 min at 50 °C[2] in solution making direct substitution strategies inappropriate as a means for synthesising functionalised, optically active derivatives. Substituted, chiral binaphthalenes are among the most widely used and useful chiral ligands and auxiliaries employed in asymmetric synthesis[3] and a number of different strategies have been employed for their preparation.[4] By far the most widely used approach involves preparation of a racemic intermediate or target compound followed by resolution of the mixture (typically via co-crystallisation or derivatisation–crystallisation). To this end, convenient and reproducible procedures have been developed for simple derivatives (such as BINOL and BINAP).

Asymmetric syntheses of substituted chiral binaphthalenes are desirable in many cases and some elegant strategies have been demonstrated.[5] For example, Meyers has employed oxazoline chiral auxiliaries in S_NAr reactions leading to binaphthalenes (Scheme 1) and high diastereoselectivity



Scheme 1. Asymmetric S_NAr approaches to chiral binaphthalenes.

Keywords: Asymmetric Suzuki coupling; Palladium; Cross-coupling; Chiral binaphthalenes; Atropisomers.
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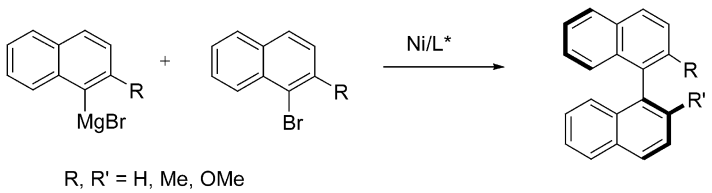


Scheme 2. Asymmetric Kumada coupling.

was achieved.[5b,c] In a somewhat complementary approach, Cram employed a chiral leaving group and also achieved high enantioselectivity.[5d,e] Although elegant, these procedures also suffer from the lack of generality and use of a stoichiometric chiral auxiliary.

An ideal procedure to binaphthalenes can be envisaged involving an asymmetric, catalytic cross-coupling reaction. Kumada reported the first such asymmetric cross-coupling reaction between 1-bromo-2-methylnaphthalene and its corresponding Grignard reagent using a nickel catalyst (Scheme 2) and modest selectivities were obtained (12.5%) using NAPHOS **2** (Fig. 1).[6] The procedure has been significantly improved by Hayashi who screened a series of chiral ligands and conditions.[7] Ees of up to 95% were achieved and the best ligand was found to be PFOMe **5**

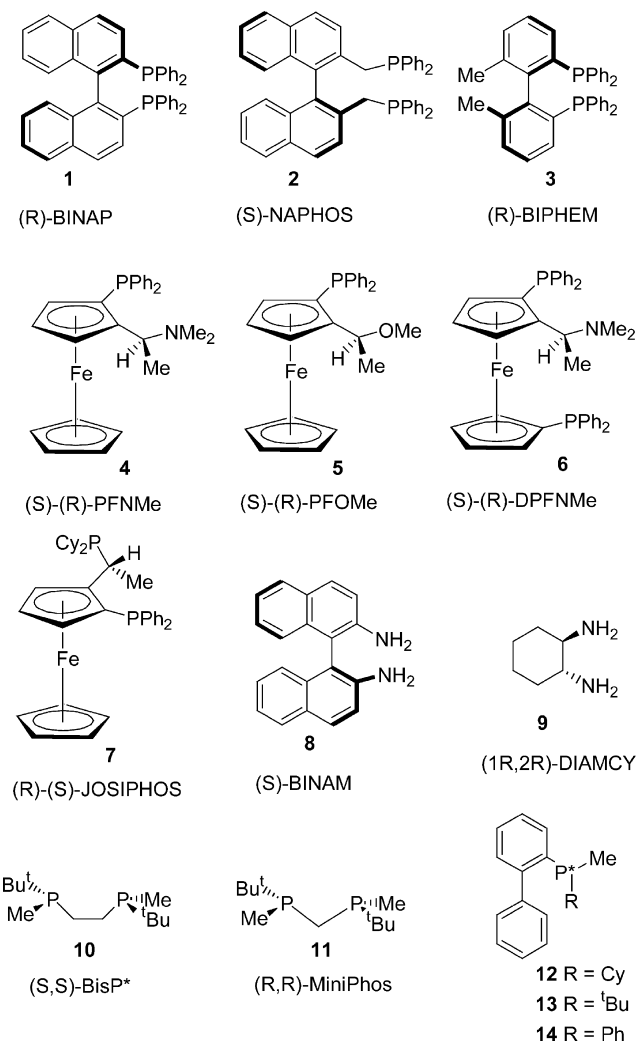


Figure 1. Chiral ligands **1**–**14**.

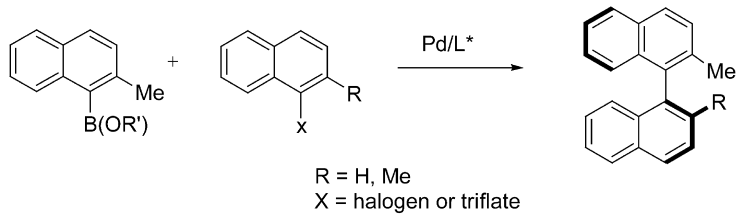
(Fig. 1). Although no definitive mechanism has been put forward, it was postulated that the methoxy group on the ligand serves to coordinate to the magnesium ion of the incoming Grignard reagent during transmetallation. The nickel catalyst in these reactions has, in some cases, been replaced by palladium. Mixed results have been obtained and the reactions give only modest ees.[8] Other approaches have involved the use of asymmetric desymmetrisation procedures.[9]

2. Results and discussion

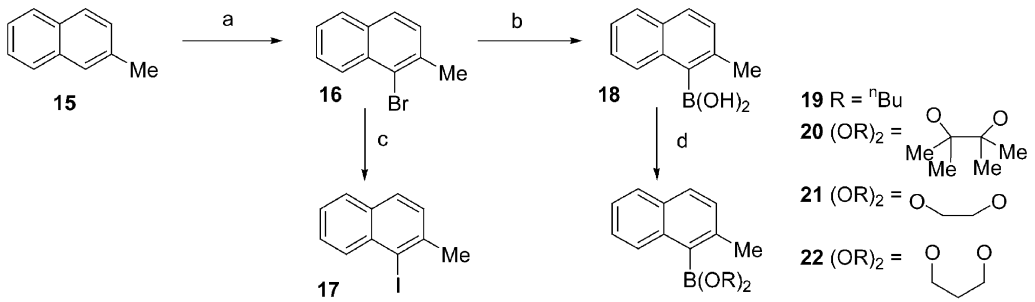
Our group was the first to describe the intermolecular asymmetric Suzuki cross-coupling reaction[10–12] and subsequent examples have been reported by others.[13] In this paper, we report details of our investigation of the synthesis of chiral biaryls (binaphthalenes) via the asymmetric Suzuki reaction. The Suzuki reaction[14] has many inherent advantages over related Ni and Pd-catalysed couplings and has become the method of choice for the synthesis of many biaryls and related products. Its advantages derive from the use of boronic acid derivatives as coupling partners (isolable compounds which are easily stored and handled). Furthermore, the Suzuki reaction (boronic acid derivatives) is compatible with a wide variety of functional groups (compared to Grignard reagents which cannot be used if one of the reactants bears an electrophile) and produces non-toxic by-products.

Simple binaphthalenes were chosen as targets for investigation of the asymmetric Suzuki reaction, not least because simple (lightly functionalised) targets represent significant challenges in asymmetric synthesis. The choice also permits direct comparison with previously reported procedures employing Grignard reagents as coupling partners and straightforward evaluation of optical purities by optical rotation (chiral HPLC is unsuitable for such lightly functionalised compounds). The general reaction is depicted in Scheme 3.

Pure 1-bromo-2-methylnaphthalene is not commercially available and its synthesis is complicated by production of an unwanted regioisomer (6-bromo) which cannot be easily removed.[15] This proved to be the case in our hands also and we were unable to isolate the pure compound. Alternative conditions were investigated and material of sufficient purity was obtained from direct bromination of 2-methylnaphthalene with NBS in acetonitrile.[16] Direct electrophilic iodination (iodine monochloride) of 2-methylnaphthalene failed to give the required iodide and the intermediate was most conveniently synthesised via metal–halogen exchange followed by iodine quench (Scheme 4).[17]



Scheme 3. General scheme for the asymmetric Suzuki reaction towards lightly functionalised binaphthalenes.

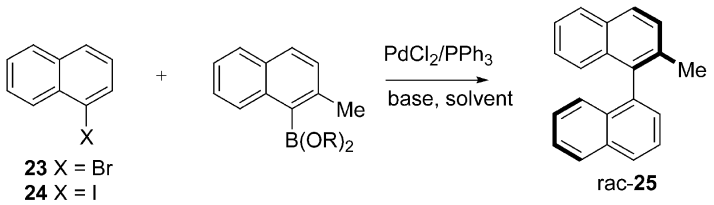


Scheme 4. Synthesis of coupling partners. Reagents: (a) NBS, acetonitrile (95%). (b) (i) Mg, THF; (ii) $BOMe_3$ (60%); (iii) H_3O^+. (c) (i) BuLi, THF, −78 °C; (ii) I_2, −78 °C–rt (74%). (d) see text.

Naphthyl boronic acids were conveniently prepared from the corresponding bromides via formation of the Grignard reagent and quenching with trimethyl borate at −78 °C. Subsequent hydrolysis and recrystallisation yielded the pure boronic acids. A series of boronate esters were prepared by treatment of the boronic acids with alcohol/diol and azeotropic removal of water (Scheme 4). It is interesting to note that attempts to prepare the boronate ester from 2-methylnaphth-1-yl boronic acid and propane diol under these conditions failed due to competing deboronation (see later).

2.1. Racemic coupling

The Suzuki coupling of sterically hindered partners remains a challenge.[14] Significant progress has been made over recent years but no general ligand/catalyst system exists.[18] Our investigation therefore started with assessment of the factors controlling successful coupling to give binaphthalenes (recognising that these 'standard' conditions would be used as the basis for subsequent modification for invention of an asymmetric version). Based on previous work on cross-coupling reactions[6c,7a,19] we chose the boronic acid



Scheme 5. Racemic Suzuki coupling to give **25**.

Table 1. Racemic Suzuki coupling to give **25**

Entry	Halide	Boron species[a]	Solvent (temperature)	Base	Time (h)	Yield (%) (conversion)
1	**23**	**18**	DME/H_2O (reflux)	$Ba(OH)_2$	17	44
2	**23**	**18**	DME (reflux)	CsF	17	72
3	**24**	**18**	Tol/EtOH/H_2O (reflux)	$Ba(OH)_2$	17	(>98)
4	**24**	**18**	DME/H_2O (reflux)	$Ba(OH)_2$	17	61
5	**24**	**18**	DME/H_2O (40 °C, ultrasound)	$Ba(OH)_2$	7	(>98)
6	**24**	**18**	DME/H_2O (50 °C)	$Ba(OH)_2$	5	(>98)
7	**24**	**18**	DME/H_2O (reflux)	$Ba(OH)_2$	5	(>98)
8	**24**	**18**	DME (reflux)	$Ba(OH)_2$	17	16
9	**24**	**18**	DME (reflux)	CsF	17	74
10	**24**	**18**	DME (reflux)	NaOH	17	36
11	**24**	**18**	Tol /crown ether (reflux)	KOH	17	19
12	**24**	**18**	Tol	K_2CO_3	17	3
13	**24**	**18**	DME/H_2O (reflux)	$Ba(OH)_2$	72	5[b]
14	**24**	**20**	DMF (reflux)	K_3PO_4	96	0
15	**24**	**20**	DME (reflux)	CsF	72	(>98)

[a] 1.1 equiv. of boron species except entries 5–7 where 2 equiv. used.
[b] Carried out with $PtCl_2$.

(derivative) as the most hindered partner for the synthesis of 2-methyl-1,1′-binaphthalene. Thus typical Suzuki coupling conditions were employed in the first instance and involved reaction of halonaphthalene with 2-methylnaphth-1-yl boronic acid or ester in the presence of 1.5–2.0 mol equiv. of base and 3 mol% $PdCl_2$/6 mol% PPh_3 in refluxing solvent. Total consumption of the boronic acid derivative was generally observed yielding a product mixture comprising target binaphthalene, halide starting material and 2-methylnaphthalene (from deboronation) (Scheme 5). Products were isolated and characterised but subsequent reaction analysis was performed by ^{1}H NMR spectroscopy of crude reaction mixtures to give an accurate assessment of product distribution. The results are summarised in Table 1. It is widely accepted that aryl iodides are superior to bromides in such coupling reactions and the same conclusion can be drawn in this case. Naphthyl iodide led to faster reaction and improved yields and was used in all subsequent experiments.

A series of experiments were then performed in both homogeneous and heterogeneous conditions to determine optimised conditions of solvent and base to minimise protonolysis of the boronic acid. Strong bases and homogeneous conditions have been reported to be effective in the coupling of sterically congested substrates and barium hydroxide is commonly employed.[20,21] We found the use of barium hydroxide in DME/water to be particularly effective in achieving the coupling but significant competing deboronation meant that 2 equiv. of boronic acid were required to achieve full conversion of the halide. Toluene/ethanol/water has been reported to be a good solvent mixture for such coupling reactions[22] and was found to give good conversions and reaction rates in our case also. The homogeneous reaction using CsF in DME gave reasonable conversions. Heterogeneous conditions employing the hindered boronic acid were, in contrast, far inferior. It is worth noting that use of platinum in place of palladium gave only a low conversion to biaryl.

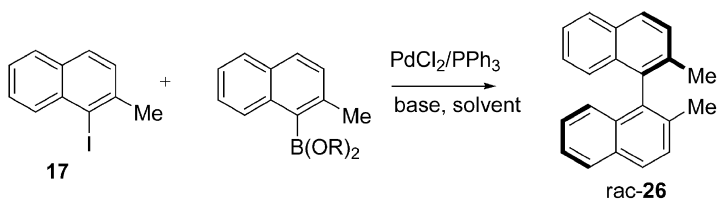
In many cases, the use of boronate esters (usually requiring anhydrous conditions) improves the Suzuki coupling of hindered substrates.[14] Pinacol boronate ester **20** coupled smoothly with iodonaphthalene to give a high conversion to the binaphthalene, albeit at a slower rate that the reaction employing the parent boronic acid.

Racemic Suzuki coupling toward 2,2′-dimethyl-1,1′-binaphthalene was performed in parallel to the above study (Scheme 6, Table 2). In this case, it was found that no coupled product was obtained when the parent boronic acid was employed (using the above optimised conditions) and complete deboronation was observed. Modest conversion (36%) of halide to binaphthalene was achieved when pinacol boronate ester **20** was employed (DME/CsF) but the reaction took 3 days to reach completion. The best results were obtained when the ethylene glycol ester was employed (69% after 6 days).

Like others, we found that efficient cross-coupling to give hindered biaryls was complicated by protonolysis (deboronation) which was frequently the dominating process. Deboronation is a slow process in the absence of palladium and is likely to occur via an Ar–Pd species.[23] In these reactions it can also be inferred that simple oxidative addition (of aryl halide to Pd(0)) is a relatively fast process independent of whether bromides or iodides are used.[23] The simple, standard mechanism for the Suzuki coupling is no longer adequate to describe such reactions and a more comprehensive mechanism is depicted in Figure 2. The key steps are transmetallation and reductive elimination. Fast reductive elimination (the process competing with hydrolysis/deboronation) is crucial to the success of the reaction and the observation that aryl iodides give faster, better reactions implies that reductive elimination is itself triggered by oxidative addition of another molecule of aryl halide.[23,24]

2.2. Asymmetric Suzuki coupling

Chiral ligands containing various features were employed in the investigation of the asymmetric Suzuki reaction and their structures are depicted in Figure 1. The general



Scheme 6. Racemic Suzuki coupling to give **26**.

Table 2. Racemic Suzuki coupling to give **26**

Entry	Halide	Boron species[a]	Solvent (reflux)	Base	Time (h)	Yield (%) (conversion)
1	**16**	**18**	DME/H_2O	Na_2CO_3	17	(Trace)
2	**16**	**18**	DME/H_2O	$Ba(OH)_2$	17	(Trace)
3	**17**	**18**	DME/H_2O	$Ba(OH)_2$	17	(Trace)
4	**17**	**18**	DME	CsF	17	(Trace)
5	**17**	**20**	DMF	K_3PO_4	96	(Trace)
6	**17**	**20**	DME	CsF	72	36
7	**17**	**19**	DME	CsF	17	0 (decomp)
8	**17**	**21**	DME	CsF	144	69

[a] 1.1 equiv. of boron species except entries 3, 4, 6–8 where 2 equiv. used.

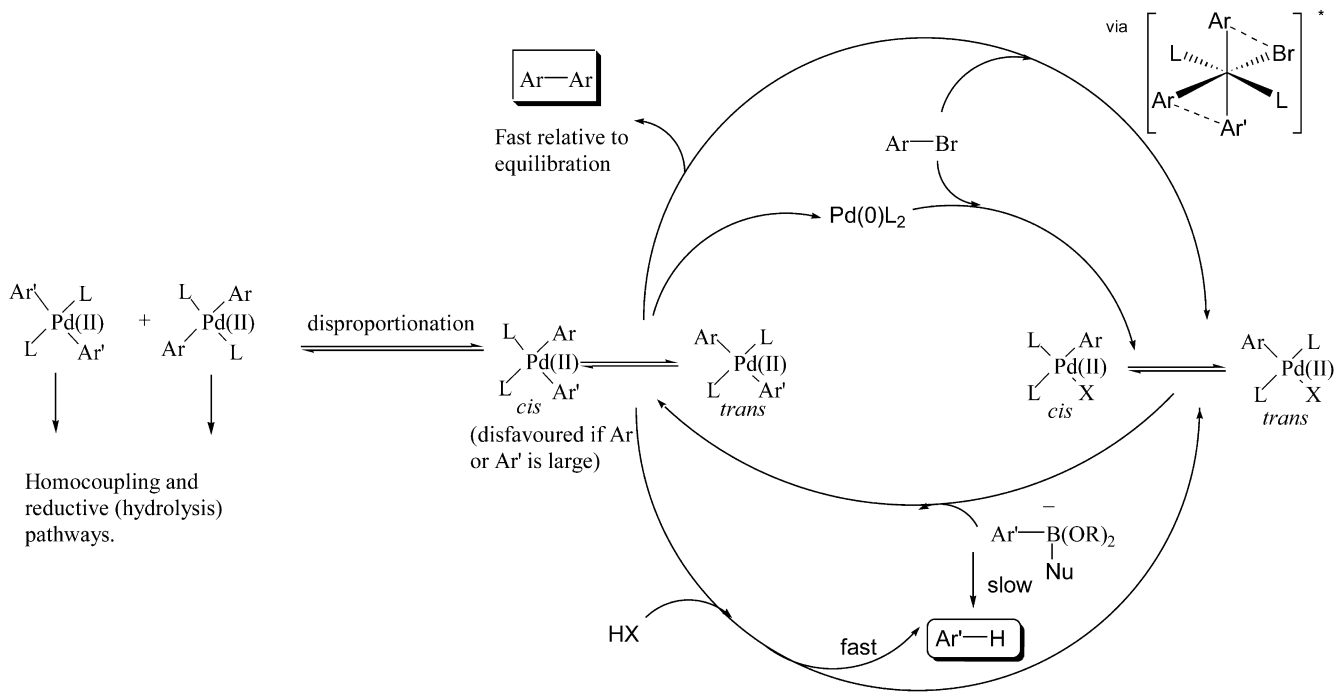
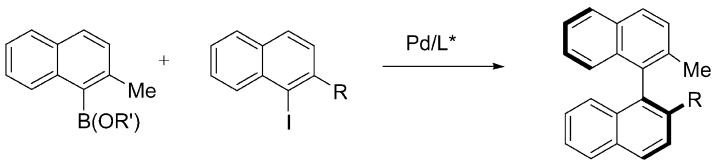


Figure 2. Mechanism for the Suzuki reaction of hindered coupling partners.

Table 3. Asymmetric Suzuki coupling to give **25** and **26**



Entry	Halide	Boron species[a]	L*[b]	Solvent (reflux)	Base	Product	Time (h)	Yield (%)	Opt. P'ty[c] (%)
1	**24**	**18**	**1**	DME/H_2O	$Ba(OH)_2$	(*S*)-(+)-**25**	17	55	25
2	**24**	**18**	**1**	DME	CsF	(*S*)-(+)-**25**	17	43	21
3	**24**	**18**	**1**	Tol/EtOH/H_2O	$Ba(OH)_2$	(*S*)-(+)-**25**	17	47	8
4	**24**	**18**	**4**	DME/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	17	44	63
5	**24**	**18**	**4**	DME/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	5	44	61
6	**24**	**18**	**4**	DME	CsF	(*R*)-(−)-**25**	17	44	55
7	**24**	**18**	**4**	Tol/EtOH/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	17	45	52
8	**24**	**18**	**5**	DME/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	2	82	2
9	**24**	**18**	**5**	DME/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	17	74	14
10	**24**	**18**	**6**	DME/H_2O	$Ba(OH)_2$	(*S*)-(+)-**25**	17	73	4
11	**24**	**18**	**7**	DME/H_2O	$Ba(OH)_2$	**25**	17	6	0
12	**24**	**18**	**10**	DME/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	17	7	4
13	**24**	**18**	**11**[d]	DME/H_2O	$Ba(OH)_2$	(*S*)-(+)-**25**	17	10	11
14	**24**	**18**	**12**	DME/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	17	54	4
15	**24**	**18**	**13**[c]	DME/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	17	40	5
16	**24**	**18**	**13**	DME/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	17	83	10
17	**24**	**18**	**14**	DME/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	17	73	24
18	**24**	**18**	**8**	DME/H_2O	$Ba(OH)_2$	**25**	17	9	0
19	**24**	**18**	**9**	DME/H_2O	$Ba(OH)_2$	—	17	0	—
20	**17**	**21**	**6**	DME	CsF	(*S*)-(+)-**26**	9 days	13	17
21	**17**	**21**	**4**	DME	CsF	(*R*)-(−)-**26**	6 days	60	85
22	**17**	**21**	**1**[e]	DME	CsF	(*S*)-(+)-**26**	5 days	21	14
23	**17**	**20**	**1**[e]	DME	CsF	(*R*)-(−)-**26**	4 days	17	10

[a] 1.1 equiv. of boron species except entries 7–9 where 2 equiv. used.
[b] Catalyst generated in situ using $PdCl_2$ and L* unless stated otherwise.
[c] Error estimated as $\leq \pm 3\%$.[25]
[d] Catalyst generated in situ using ($PdClC_3H_5$) and L*.
[e] Preformed complex.

conditions used for the asymmetric coupling were derived from the previous investigation of the corresponding racemic synthesis. The procedure involved treating 1-iodonaphthalene with 1.1–2.5 equiv. of 2-methylnaphth-1-yl boronic acid or boronate ester in refluxing solvent using 1.5–2 equiv. of base (homogeneous conditions) and 3 mol% $PdCl_2$/3 or 6 mol% chiral ligand. Binaphthalenes were isolated by column chromatography using carefully distilled hexane. Moreover, recrystallisation was not performed in order to avoid fractionation leading to erroneous results. Optical purities were determined by optical rotation (suitable conditions for chiral HPLC were not found).

In the first instance, the asymmetric Suzuki reaction leading to 2-methyl-1,1′-biphaphthalene was investigated and the results are summarised in Table 3. As expected, diamine ligands BINAM **8** and DIAMCY **9** (Fig. 1) gave only racemic product in poor yield. Modest selectivity (19–25% ee[25]) was observed when phosphine ligand BINAP **1** was employed. The selectivity drops when the solvent was changed from DME to toluene/ethanol/water.

Ligand PFOMe **5** proved to be excellent for the comparable asymmetric Kumada coupling employing the Grignard reagent in place of boronic acid.[7a] Poor selectivity was observed when this ligand was employed in the asymmetric Suzuki reaction (optical purity 2–14%). This observation is consistent with the suggestion that the methoxy group serves to deliver (in an asymmetric fashion) the organometallic during transmetallation.[7a] Such interactions are expected to be much stronger for the Grignard reagent. Ligand PFNMe **4** (in which the methoxy group of PFOMe **5** is replaced by NMe_2) was therefore used and found to improve selectivity in the reaction dramatically (giving optical purities up to 63%). It is interesting to note that this ligand is ineffective in the related Kumada coupling. Selectivity was significantly reduced when bisphosphine ligands JOSIPHOS **7** and DPFNMe **6** were used and this observation is consistent with the results obtained with Grignard reagents.

Selected syntheses of 2,2′-dimethyl-1,1′-binaphthalene were also investigated (using boronate esters). Once again, modest selectivities were observed when BINAP **1** and DPFNMe ligands were used. Ligand PFNMe again proved the best of all studied (in terms of both yield and selectivity) and gave the highest observed optical purity of 85%.

A selection of P-chiral ligands were also screened. BisP* **10**[26] and MiniPhos **11**[27] proved ineffective in the asymmetric Suzuki reaction giving both poor yields and optical purities. As expected the use of biphenylphosphine ligands **12**–**14**[28] led to good conversions but optical purities were again low. This observation reinforces the conclusion[10,13a] that P–N ligands provide the best combination for good yields and selectivity and it is reasonable to speculate that the amine nitrogen serves to deliver the boronate and the key step of the mechanism is transmetallation.

A closer inspection of our results hint at some surprising subtleties. Most striking is the observation that opposite enantiomers can result from (otherwise) identical reactions employing different boronates (the pinocol boronate ester **20** gives the opposite enantiomer to the ethylene glycol boronate **21**). The conclusion must be that the reaction is operating under kinetic control (thermodynamic control would lead to the same optical purity and stereochemistry independent of boronate) and again this suggests that the important step controlling asymmetry is the transmetallation. The Suzuki coupling leading to methoxybinaphthalenes has also been shown to give unexpected results and inversion of stereochemical outcome has been observed as a function of Pd/ligand ratio.[13b] The assumption is usually made that reductive elimination is slow (with respect to equilibration of the intermediate complex) when sterically hindered partners are used in the Suzuki coupling. However, it would appear that this is not the case and the intermediate complex undergoes reductive elimination faster than equilibration (epimerisation or via *cis*–*trans* isomerisation).

3. Conclusion

The asymmetric Suzuki coupling can be used to synthesise lightly functionalised binaphthalenes in reasonable yields and optical purities. As with many couplings involving sterically hindered partners, the reactions are complicated by competing protonolysis (deboronation). Indeed, in the most severe case (synthesis of 2,2′-dimethyl-1,1′-binaphthalene) successful coupling could only be achieved using homogeneous conditions and boronate esters. It is clear that the simple, standard mechanism is inadequate when describing the Suzuki coupling of hindered partners. There is strong evidence that the key step leading to asymmetry is transmetallation (delivery of the organometallic by the asymmetric ligand) and the reactions operate under kinetic control. Reductive elimination (itself likely to be triggered by oxidative addition of another molecule of halide) is fast compared with equilibration (epimerisation and/or *cis*–*trans* isomerisation).

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at 270 MHz on a Jeol EX270 FT or at 300 MHz on a Varian 300 spectrometer in $CDCl_3$, unless otherwise stated. Signals are quoted in ppm as δ downfield from tetramethylsilane (δ 0.00) as internal standard. ^{13}C NMR spectra were recorded at 67.9 MHz or 75.4 MHz on the same spectrometers, respectively and in the same solvent. IR spectra were recorded on a Perkin–Elmer 1720X FT-IR spectrophotometer as neat liquid films or nujol mulls for solid materials.

Elemental analyses and low resolution electron impact mass spectra were performed by Mr. A. W. R. Saunders at the University of East Anglia on a Kratos model MS25 magnetic sector mass spectrometer using electron impact ionisation (EI, 70 eV). Analytical data are quoted to the nearest 0.01%. Additional mass spectra were obtained via the EPSRC National Mass Spectroscopy Service Centre at the University of Wales at Swansea. Melting points are

uncorrected and recorded using a Kofler hot-stage melting point apparatus with a digiton model 2751-K display.

Optical rotations were measured on a Perkin–Elmer model 141 polarimeter or on a Jasco DIP-370 digital polarimeter in the solvents stated (HPLC-grade), and $[\alpha]_D$ units are recorded in 10^{-1} deg cm^2 g^{-1} using the sodium lamp at 589 nm.

Reaction solvents were dried and distilled prior to use following standard procedures. Other solvents were SLR-grade and used without drying, unless stated otherwise. Temperatures quoted in the reaction conditions are the temperatures of the reaction mixture, and not the cooling or heating bath.

4.1.1. 2-Methylnaphth-1-yl boronic acid 18. The Grignard reagent of 1-bromo-2-methylnaphthalene **16** was prepared following the experimental procedure described by Miyano.[29] A solution of 1-bromo-2-methylnaphthalene **16** (10 g, 45.2 mmol) in dry THF (20 mL) was added in small portions to a suspension of dry magnesium turnings (1.1 g, 45.2 mmol) and a crystal of iodine in dry THF (10 mL) at room temperature under nitrogen. Once the reaction had started, the bromide was added at such a rate to maintain a gentle reflux. The mixture was heated under gentle reflux for 2 h then cooled to room temperature. The Grignard reagent was transferred in small portions to a solution of trimethyl borate (10.3 mL, 90.40 mmol) in dry THF (20 mL) at −78 °C. This mixture was gradually warmed to room temperature and stirred overnight. Dilute HCl (2 N, 40 mL) was added and the two layers were separated. The aqueous layer was extracted with diethyl ether (2×50 mL). The combined organic layers were washed with water (2×80 mL), dried, filtered and the solvent evaporated under reduced pressure. The cream powder (7.67 g, 91%) was recrystallised from toluene to give the title compound (5.19 g, 60% from 1-bromo-2-methylnaphthalene **16**) as a white powder, mp 90.0–92.5 °C (toluene). (Found: C, 71.11; H, 5.95. $C_{11}H_{11}BO_2$ requires: C, 71.02; H, 5.96%); ν_{max} (Nujol)/cm^{-1} 3302 (br, OH); δ_H (300 MHz; $CDCl_3$) 2.59 (3H, s), 4.85 (2H, s), 7.32 (1H, d, J=8.2 Hz), 7.42–7.48 (2H, m) and 7.76–7.87 (3H, m); δ_C (75.4 MHz) (*C*–B is not observed) 22.4, 125.0, 126.3, 127.4, 128.3, 128.3, 128.9, 131.3, 135.1 and 138.2; EIMS *m*/*z* 186 (M^+, 100%) and 141 ($M^+-B(OH)_2$, 53).

4.2. General procedure for the preparation of boronate esters 19–21

A solution of 2-methylnaphth-1-yl boronic acid **18**, diol (alcohol) and toluene was heated under reflux with azeotropic removal of water using a Dean–Stark type separator. The reaction was monitored by TLC and, when complete (typically 2–4 h), the solvent was removed under reduced pressure. Dichloromethane (20 mL) and water (20 mL) were added to the residue and the layers separated. The aqueous layer was extracted with dichloromethane (2×20 mL) and the combined organic layers washed with water (2×20 mL), dried, filtered and the solvent evaporated under reduced pressure to give the crude boronate.

4.2.1. 2-Methylnaphth-1-yl(butanol)boronate ester 19. 2-Methylnaphth-1-yl boronic acid **18** (0.5 g, 2.69 mmol), *n*-butanol (0.80 g, 5.38 mmol) and toluene (10 mL) were heated under reflux for 4 h with regular addition of butanol and worked up according to the general procedure to give the title compound as a colourless oil (0.75 g, 94%); δ_H (300 MHz; $CDCl_3$) 0.89 (6H, t, J=7.3 Hz), 1.38 (4H, m), 1.57 (4H, m), 2.50 (3H, s), 3.83 (4H, t, J=7.3 Hz), 7.31 (1H, d, J=8.3 Hz), 7.40–7.46 (2H, m), 7.65 (1H, d, J=8.1 Hz), 7.76 (1H, d, J=9.0 Hz) and 7.81 (1H, d, J=7.5 Hz). This compound was unstable over a short period of time at room temperature and was therefore used immediately.

4.2.2. 2-Methylnaphth-1-yl(pinacol)boronate ester 20. 2-Methylnaphth-1-yl boronic acid **18** (2.5 g, 13.45 mmol), pinacol (1.59 g, 13.45 mmol) and toluene (40 mL) were heated under reflux for 4 h and worked up according to the general procedure. The crude product was purified by column chromatography over silica gel (eluting with dichloromethane) to give the title compound as a colourless semi-solid (3.1 g, 86%). δ_H (300 MHz; $CDCl_3$) 1.49 (12H, s,), 2.63 (3H, s), 7.29 (1H, d, J=8.5 Hz), 7.37–7.45 (2H, m), 7.73–7.78 (2H, m) and 8.11 (1H, d, J=8.4 Hz); δ_C (75.4 MHz) (*C*–B is not observed) 22.6, 25.1 (4 C), 84.0 (2 C), 124.5, 125.9, 127.5, 128.1, 128.4, 129.5, 131.3, 136.6 and 141.3; EIMS *m*/*z* 268 (M^+, 83%) and 141 ($M^+-B(OC(CH_3)_2C(CH_3)_2O$, 24).

4.2.3. 2-Methylnaphth-1-yl(ethylene glycol)boronate ester 21. 2-Methylnaphth-1-yl boronic acid **18** (2 g, 10.76 mmol), ethylene glycol (760 mg, 11.84 mmol) and toluene (25 mL) were heated under reflux for 2 h and worked up according to the general procedure. The oil obtained crystallised after a few days to give the title compound (2.14 g, 94%) as a white solid, mp 50.2–52.2 °C. (Found: C, 73.65; H, 6.16. $C_{13}H_{13}O_2B$ Requires: C, 73.64; H, 6.18%); δ_H (300 MHz; $CDCl_3$) 2.64 (3H, s), 4.55 (4H, s), 7.34 (1H, d, J=8.4 Hz), 7.39–7.50 (2H, m), 7.81 (2H, d, J=8.1 Hz) and 8.16 (1H, d, J=8.3 Hz); δ_C (75.4 MHz) (*C*–B is not observed) 22.9, 65.8 (2 C), 124.8, 126.1, 127.9, 128.2, 128.6, 130.0, 131.4, 136.8 and 142.1; EIMS *m*/*z* 212 (M^+, 100%) and 141 ($M^+-B(OR)_2$, 21).

4.3. General procedure for Suzuki couplings

A round bottom flask containing solid materials, i.e. 2-methylnaphth-1-yl boronic acid or boronate ester, base (amount calculated with reference to the boronic acid), palladium chloride and ligand (both amounts calculated with reference to the halide derivative) was purged under nitrogen without any solvent for 10 min. A solution of naphthyl halide in solvent was injected and the mixture stirred for several hours under reflux and nitrogen (oil bath previously heated to obtain reflux as soon as all the reagents were mixed). The solvent was removed under reduced pressure and dichloromethane and water were added. The layers were separated and the aqueous layer extracted with dichloromethane. The combined organic layers were washed with water, dried, filtered and the solvent evaporated under reduced pressure. The crude product was typically purified by column chromatography over silica gel.

4.3.1. Racemic couplings

4.3.1.1. (±)-2-Methyl-1,1′-binaphthalene 25[29]—representative procedure (Table 1, entry 4). 2-Methylnaphth-1-yl

boronic acid **18** (0.8 g, 4.33 mmol), barium hydroxide octahydrate (1.86 g, 5.91 mmol), palladium chloride (20.9 mg, 0.12 mmol), triphenylphosphine (61.9 mg, 0.24 mmol), 1-iodonaphthalene **24** (1 g, 3.94 mmol), DME (25 mL) and water (4 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with petroleum ether) to give the title compound (645 mg, 61%) as a white solid, mp 82.8–87.1 °C (lit.,[29] 86–88 °C; δ_H (300 MHz; $CDCl_3$) 2.11 (3H, s), 7.13–7.65 (8H, m), 7.61 (1H, dd, J=7.0, 1.3 Hz), 7.88 (2H, d, J=8.4 Hz) and 7.96 (2H, d, J=8.4 Hz); δ_C (67.9 MHz) 20.4, 124.9, 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, 133.556, 133.8, 134.5, 136.2 and 137.6.

4.3.1.2. (±)-2,2′-Dimethyl-1,1′-binaphthalene 26[30]—representative procedure (Table 2, entry 6). 2-Methylnaphth-1-yl(pinacol)boronate ester **20** (0.22 g, 0.82 mmol), cesium fluoride (0.25 g, 1.64 mmol), palladium chloride (2.2 mg, 0.01 mmol), triphenylphosphine (6.5 mg, 0.02 mmol), 1-iodo-2-methylnaphthalene **17** (0.15 g, 0.41 mmol) and DME (5 mL) were heated under reflux for 3 days and worked up according to the general procedure. The brown oil was purified by column chromatography over silica gel (eluting with petroleum ether) to give the title compound (86 mg, 36%) as a colourless oil; δ_H (300 MHz; $CDCl_3$) 1.96 (6H, s), 6.90 (2H, d, J=8.3 Hz), 7.13 (2H, m), 7.32 (2H, m), 7.44 (2H, d, J=8.4 Hz) and 7.82 (4H, dd, J=7.4, 4.1 Hz).

4.3.2. Asymmetric couplings. Optical purities were determined by optical rotation; 2-methyl-1,1′-binaphthalene **25** lit.,[7a] $[\alpha]_D^{22}=-43.9$ (c 1.0, $CHCl_3$); 2,2′-dimethyl-1,1′-binaphthalene **26** (lit.,[7a] $[\alpha]_D^{22}=-35.6$ (c 1.0, $CHCl_3$), lit.,[29] $[\alpha]_D^{22}=-19.0$ (c 1.3, ethanol)).

4.3.2.1. 2-Methyl-1,1′-binaphthalene 25—representative procedures.

(a) With (*R*)-(+)-BINAP 1.

Using $Ba(OH)_2{\cdot}8H_2O$/DME/H_2O (Table 3, entry 1). 2-Methylnaphth-1-yl boronic acid **18** (0.4 g, 2.17 mmol), barium hydroxide octahydrate (0.93 g, 2.96 mmol), [(*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]palladium(II) chloride **1** (47.3 mg, 0.06 mmol), 1-iodonaphthalene **24** (0.5 g, 1.97 mmol), DME (12 mL) and water (3 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil (0.56 g) was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (290 mg, 55%) as a white solid, $[\alpha]_D^{22}=+10.9$ (c 0.36, $CHCl_3$), optical purity 25%.

Using CsF/DME (Table 3, entry 2). 2-Methylnaphth-1-yl boronic acid **18** (0.18 g, 0.87 mmol), cesium fluoride (0.24 g, 1.57 mmol), [(*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]palladium(II) chloride **1** (18.9 mg, 0.02 mmol), 1-iodonaphthalene **24** (0.2 g, 0.79 mmol) and DME (5 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (90 mg, 43%) as a white solid, $[\alpha]_D^{22}=+9.1$ (c 0.22, $CHCl_3$), optical purity 21%.

Using $Ba(OH)_2{\cdot}8H_2O$/toluene/EtOH/H_2O (Table 3, entry 3). 2-Methylnaphth-1-yl boronic acid **18** (0.18 g, 0.87 mmol), barium hydroxide octahydrate (0.37 g, 1.19 mmol), [(*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]palladium(II) chloride **1** (18.9 mg, 0.02 mmol), 1-iodonaphthalene **24** (0.2 g, 0.79 mmol), toluene (3 mL), ethanol (3 mL) and water (1 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (100 mg, 47%) as a white solid, $[\alpha]_D^{22}=+3.4$ (c 0.37, $CHCl_3$), optical purity 8%.

(b) With (+)-(*S*)-(*R*)-PFNMe **4**.

Using $Ba(OH)_2{\cdot}8H_2O$/DME/H_2O (Table 3, entry 4). 2-Methylnaphth-1-yl boronic acid **18** (0.24 g, 1.3 mmol), barium hydroxide octahydrate (0.56 g, 1.77 mmol), palladium chloride (6.3 mg, 0.03 mmol), (+)-(*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-diphenylphosphino)ferrocenyl]ethylamine **4** (31.3 mg, 0.06 mmol), 1-iodonaphthalene **24** (0.3 g, 1.18 mmol), DME (7 mL) and water (2 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil (0.38 g) was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (144 mg, 44%) as a white solid, $[\alpha]_D^{22}=-27.7$ (c 0.39, $CHCl_3$), optical purity 63%.

Using CsF/DME (Table 3, entry 6). 2-Methylnaphth-1-yl boronic acid **18** (0.44 g, 2.36 mmol), cesium fluoride (0.72 g, 4.72 mmol), palladium chloride (6.3 mg, 0.04 mmol), (+)-(*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-diphenylphosphino)ferrocenyl]ethylamine **4** (31.3 mg, 0.07 mmol), 1-iodonaphthalene **24** (0.3 g, 1.18 mmol) and DME (7 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (138 mg, 44%) as a white solid, $[\alpha]_D^{22}=-24.2$ (c 0.38, $CHCl_3$), optical purity 55%.

Using $Ba(OH)_2{\cdot}8H_2O$/toluene/EtOH/H_2O (Table 3, entry 7). 2-Methylnaphth-1-yl boronic acid **18** (0.18 g, 0.87 mmol), barium hydroxide octahydrate (0.37 g, 1.18 mmol), palladium chloride (4.2 mg, 0.02 mmol), (+)-(*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-diphenylphosphino)ferrocenyl]ethylamine **4** (20.8 mg, 0.05 mmol), 1-iodonaphthalene **24** (0.2 g, 0.79 mmol) and toluene (3 mL), ethanol (3 mL) and water (1 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (94 mg, 45%) as a white solid, $[\alpha]_D^{22}=-22.8$ (c 0.35, $CHCl_3$), optical purity 52%.

(c) With (+)-(*S*)-(*R*)-PFOMe 5 (Table 3, entry 9).

2-Methylnaphth-1-yl boronic acid **18** (0.34 g, 1.82 mmol), barium hydroxide octahydrate (0.86 g, 2.72 mmol), palladium chloride (4.8 mg, 0.03 mmol), (+)-(*S*)-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethyl methyl ether **5** (23.3 mg, 0.06 mmol), 1-iodonaphthalene **24** (0.23 g,

0.91 mmol), DME (5 mL) and water (2 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil (0.32 g) was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (180 mg, 74%), $[\alpha]_D^{22}=-6.3$ (*c* 0.39, $CHCl_3$), optical purity 14%.

(d) With (+)-(*S*)-(*R*)-DPFNMe **6** (Table 3, entry 10).

2-Methylnaphth-1-yl boronic acid **18** (0.24 g, 1.30 mmol), barium hydroxide octahydrate (0.62 g, 1.95 mmol), palladium chloride (6.3 mg, 0.03 mmol), (+)-(*S*)-*N*,*N*-dimethyl-1-[(*R*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine **6** (21.9 mg, 0.03 mmol), 1-iodonaphthalene **24** (0.3 g, 1.18 mmol), DME (7 mL) and water (2 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil (0.52 g) was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (230 mg, 73%) as a white solid, $[\alpha]_D^{22}=+1.9$ (*c* 0.42, $CHCl_3$), optical purity 4%.

(e) With (*S*)-(−)-BINAM **8** (Table 3, entry 18).

2-Methylnaphth-1-yl boronic acid **18** (0.24 g, 1.30 mmol), barium hydroxide octahydrate (0.62 g, 1.95 mmol), palladium chloride (6.3 mg, 0.04 mmol), (*S*)-(−)-diamino-1,1′-binaphthalene **8** (20.2 mg, 0.07 mmol), 1-iodonaphthalene **24** (0.3 g, 1.18 mmol), DME (7 mL) and water (2 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (30 mg, 9%) as a white solid, $[\alpha]_D^{22}=0$ (*c* 0.22, $CHCl_3$), optical purity 0%.

4.3.2.2. 2,2′-Dimethyl-1,1′-binaphthalene 26.

(a) With (+)-(*S*)-(*R*)-DPFNMe **6** (Table 3, entry 20).

2-Methylnaphth-1-yl(ethylene glycol)boronate ester **21** (0.45 g, 2.07 mmol), cesium fluoride (0.62 g, 4.14 mmol), palladium chloride (4.4 mg, 0.02 mmol), (+)-(*S*)-*N*,*N*-dimethyl-1-[(*R*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine **6** (15 mg, 0.04 mmol), 1-iodo-2-methylnaphthalene **17** (0.3 g, 0.83 mmol) and DME (10 mL) were heated under reflux for 9 days (addition of chiral Pd-catalyst every 24 h) and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (60 mg, 13%) as a colourless solid, $[\alpha]_D^{22}=+5.9$ (*c* 0.22, $CHCl_3$), optical purity 17%.

(b) With (+)-(*S*)-(*R*)-PFNMe **4** (Table 3, entry 21).

2-Methylnaphth-1-yl(ethylene glycol)boronate ester **21** (0.45 g, 2.07 mmol), cesium fluoride (0.62 g, 4.14 mmol), palladium chloride (4.4 mg, 0.02 mmol), (+)-(*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-diphenylphosphino)ferrocenyl]ethylamine **4** (21 mg, 0.04 mmol), 1-iodo-2-methylnaphthalene **17** (0.30 g, 0.83 mmol) and DME (10 mL) were heated under reflux for 6 days (addition of chiral Pd-catalyst every 24 h) and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (140 mg, 60%) as a white solid, $[\alpha]_D^{22}=-16.1$ (*c* 0.31, ethanol), optical purity 85%.

(c) With (*R*)-(+)-BINAP **1**.

Using 2-methylnaphth-1-yl(ethylene glycol)boronate ester **21** (Table 3, entry 22). 2-Methylnaphth-1-yl(ethylene glycol)boronate ester **21** (0.45 g, 2.07 mmol), cesium fluoride (0.62 g, 4.14 mmol), [(*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]palladium(II) chloride **1** (19.2 mg, 0.02 mmol), 1-iodo-2-methylnaphthalene **17** (0.3 g, 0.83 mmol) and DME (10 mL) were heated under reflux for 5 days (addition of chiral Pd-catalyst every 24 h) and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (50 mg, 21%) as a colourless solid, $[\alpha]_D^{22}=+5.1$ (*c* 0.14, $CHCl_3$), optical purity 14%.

Using 2-methylnaphth-1-yl(pinacol)boronate ester **20** (Table 3, entry 23). 2-Methylnaphth-1-yl(pinacol)boronate ester **20** (0.40 g, 1.50 mmol), cesium fluoride (0.45 g, 3 mmol), [(*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]palladium(II) chloride **1** (17.9 mg, 0.02 mol), 1-iodo-2-methylnaphthalene **17** (0.27 g, 0.75 mmol) and DME (7 mL) were heated under reflux for 4 days (addition of further aliquots of chiral Pd-catalyst every 24 h) and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (35.3 mg, 17%) as a colourless solid, $[\alpha]_D^{22}=-3.68$ (*c* 0.35, $CHCl_3$), optical purity 10%.

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