The first asymmetric Suzuki cross-coupling reaction

Andrew N. Cammidge* and Karen V. L. Crépy

School of Chemical Sciences, University of East Anglia, Norwich, UK NR4 7TJ

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The first asymmetric coupling reactions between aryl halides and aryl boronates (Suzuki coupling) are described to give binaphthalene derivatives in up to 85% ee.

Restricted rotation around the aryl–aryl bond in biaryls can lead to the phenomenon of atropisomerism (sometimes called helical chirality). Chiral binaphthalenes constitute an important class of such atropisomeric compounds, not least because they are amongst the most useful chiral ligands and auxiliaries employed in asymmetric synthesis.[1] Transition metal-catalysed cross-coupling between organometallic species and aryl halides (for example) is a powerful synthetic tool and represents one of the most straightforward methods for aryl–aryl carbon–carbon bond formation.

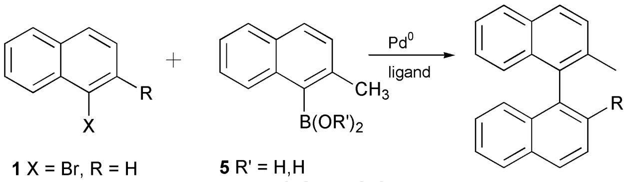
A small number of asymmetric biaryl syntheses have been reported. High selectivity has been achieved in the asymmetric synthesis of 2,2′-dimethyl-1,1′-binaphthalene **9** using chiral auxiliaries (chiral oxazoline[2,3] or a chiral leaving group[4]) or using chiral catalysts.[5] However, variable results have been reported depending on the nature of the catalyst used (*e.g.* Ni or Pd) and in all cases a Grignard reagent is used as the organometallic component.

Here we report the first examples of an *asymmetric* Suzuki coupling protocol for the construction of binaphthalenes.[6] The Suzuki coupling reaction has many inherent advantages over related Ni- and Pd-catalysed couplings and has found widespread application in the synthesis of simple and complex biaryls. The main advantage is its tolerance of a broad range of functional groups and its non-toxic by-products.[7] The organometallic partner in the Suzuki coupling (an organoboronic acid derivative) is thermally stable, inert to air and water (which allows its handling without special precautions) and unreactive to many of the electrophilic functional groups which cannot be employed (unprotected) in conjunction with Grignard reagents.

In our investigation of the asymmetric Suzuki reaction, we chose the synthesis of substituted binaphthalenes to allow comparison with previously reported methods (Scheme 1). Naphthyl halide starting materials **1–4** were obtained commercially or synthesised following standard procedures.[8] Boronic acid **5** was synthesised by converting the corresponding naphthyl bromide **3** into its Grignard reagent,[9] quenching with trimethylborate and aqueous acidic work-up. Boronic acid **5** was also converted to boronate esters **6** and **7** by treatment with pinacol and ethylene glycol respectively (Dean–Stark trap).

It is well known that use of sterically congested coupling partners can lead to poor yields in Suzuki reactions.[7,10] Racemic coupling was therefore first performed to optimise the reaction conditions (base–solvent combinations, heterogeneous *vs.* homogeneous conditions, boronic acid *vs.* boronate esters *etc.*) and selected results are summarised in Table 1. Both homogeneous and heterogeneous conditions were established to allow isolation of binaphthalenes **8** and **9** in acceptable yields. Optimum conditions typically involved treating aryl halides **1–4** with 1.1–2 mol eq. of boronic acid **5** or boronate esters **6**, **7** in the presence of 3 mol% $PdCl_2$/6 mol% PPh_3[11] and 1.5–2 mol eq. of base at elevated temperatures.[12] Competing deboronation was observed when the sterically congested boronic acids were reacted with hindered aryl halides and coupling was only observed in these cases when boronate esters were used. As expected, reactions with 1-iodonaphthalenes proved faster and led to greater yields than those reactions employing 1-bromonaphthalenes, especially with the combination $Ba(OH)_2$–DME–H_2O[12a] (Table 1, entries 1 and 4).

Our best conditions were then extended to investigation of the asymmetric Suzuki reaction using chiral ligands. Diamine ligands (*e.g.* **11**) gave racemic products but selectivity was



1 X = Br, R = H
2 X = I, R = H
3 X = Br, R = CH_3
4 X = I, R = CH_3

5 R' = H,H
6 R' = $-C(CH_3)_2-C(CH_3)_2-$
7 R' = $-CH_2CH_2-$

8 R = H
9 R = CH_3

Scheme 1 Binaphthalene synthesis *via* Suzuki coupling.

Table 1 Results from racemic Suzuki coupling

Entry	Halide	Boronic acid derivative	Product	Base/solvent[a]	Yield % (conversion[d])
1	**1**	**5**	**8**	$Ba(OH)_2$–DME–H_2O	44
2	**1**	**5**	**8**	CsF–DME	72
3	**2**	**5**	**8**	$Ba(OH)_2$–tol–EtOH–H_2O	(>98)
4	**2**	**5**	**8**	$Ba(OH)_2$–DME–H_2O	61
5	**2**	**5**	**8**	$Ba(OH)_2$–DME–H_2O[b]	(>98)
6	**2**	**5**	**8**	CsF–DME	74
7	**2**	**5**	**8**	NaOH–DME	36
8	**2**	**6**	**8**	CsF–DME[c]	(>98)
9	**3**	**5**	**9**	Na_2CO_3–DME–H_2O	(trace[e])
10	**3**	**5**	**9**	$Ba(OH)_2$–DME–H_2O	(trace[e])
11	**4**	**5**	**9**	$Ba(OH)_2$–DME–H_2O	(trace[e])
12	**4**	**5**	**9**	CsF–DME	(trace[e])
13	**4**	**6**	**9**	CsF–DME[c]	36
14	**4**	**7**	**9**	CsF–DME[c]	69

[a] Reaction time 17–19 h. [b] Carried out at 50 °C for 5 h and with 2 eq. of boronic acid. [c] Reaction time 3–6 d. [d] Determined by ^1H-NMR. The only side product observed was from deboronation. [e] The product from deboronation was observed.

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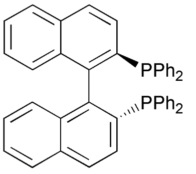
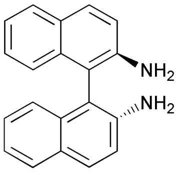
Table 2 Results from asymmetric Suzuki coupling.

Entry	Halide	Boronate	Ligand[a]	Product	Base	Solvent	Time, h	ee[b] %, (yield[c] %)
1	**2**	**5**	**13**	R-(−)-**8**	Ba(OH)$_2$	DME–H$_2$O	19	63 (44)
2	**2**	**5**	**13**	R-(−)-**8**	CsF	DME	19	55 (44)
3	**2**	**5**	**13**	R-(−)-**8**	Ba(OH)$_2$	Toluene–EtOH–H$_2$O	19	52 (45)
4	**2**	**5**	**10**	S-(+)-**8**	Ba(OH)$_2$	DME–H$_2$O	19	25 (55)
5	**2**	**5**	**10**	S-(+)-**8**	CsF	DME	19	21 (43)
6	**2**	**5**	**10**	S-(+)-**8**	Ba(OH)$_2$	Toluene–EtOH–H$_2$O	19	8 (47)
7	**2**	**5**	**12**	R-(−)-**8**	Ba(OH)$_2$	DME–H$_2$O	19	14 (74)
8	**2**	**5**	**14**	S-(+)-**8**	Ba(OH)$_2$	DME–H$_2$O	19	4 (73)
9	**2**	**5**	**11**	**8**	Ba(OH)$_2$	DME–H$_2$O	19	0 (9)
10	**4**	**7**	**13**	R-(−)-**9**	CsF	DME	6 days	85 (50)
11	**4**	**7**	**14**	S-(+)-**9**	CsF	DME	9 days	17 (13)
12	**4**	**7**	**10**	S-(+)-**9**	CsF	DME	5 days	14 (21)
13	**4**	**6**	**10**	R-(−)-**9**	CsF	DME	4 days	10 (17)

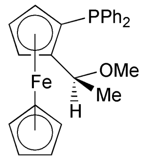
[a] Carried out with 1.1–2 eq. of boronic acid derivative in refluxing solvent using 3 mol% PdCl$_2$/6 mol% monophosphine chiral ligand or 3 mol% PdCl$_2$/3 mol% bidentate chiral ligand. [b] ee's were determined by optical rotation measurements[5b,13]. [c] Products isolated by column chromatography. To avoid fractionation, recrystallisation was not performed.



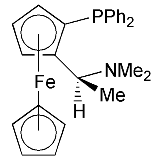
10
(*R*)-(+)-BINAP



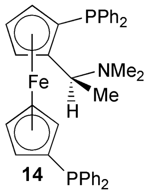
11
(*R*)-(+)-BINAM



12
(*S*)-(*R*)-PFOMe



13
(*S*)-(*R*)-PFNMe



14
(*S*)-(*R*)-DPFNMe

observed when phosphine ligands were employed. BINAP **10** led to modest ee's of 8–25% (summarised results are reported in Table 2). Furthermore, use of different boronate esters led to different selectivity (use of bulky pinacol ester **6** gave the opposite enantiomer to that observed when the boronic acid **5** or ethylene glycol ester **7** was employed (Table 2, entries 5, 12 and 13)) implying kinetic control. Highest selectivity was observed when a mono-phosphine ligand was employed. Diastereomeric ferrocene **12**, which has diphenyl phosphine and ether ligands gave disappointing ee's when **2** and **5** were coupled (**12** was found to be far superior to binaphthalene ligands in asymmetric couplings employing Grignard reagents[5b]). The related ligand **13**, in which a tertiary amine replaces the methoxide of **12**, was found to lead to the highest selectivity. With this ligand 2-methyl-1-1′-binaphthalene **8** could be synthesised in yields of 44–55% and ee's of 52–63%. The dimethyl derivative **9** gave the highest observed ee (85%) when boronate ester **7** was employed.

Our results obtained for the asymmetric Suzuki coupling can be compared to the nickel- and palladium-catalysed couplings of Grignard reagents with naphthyl halides. In the nickel-catalysed reaction, ligand **12** gives the highest ee and coupling reactions using **13** were ineffective. The selectivity in this reaction was suggested to arise through complexation of the magnesium ion of the Grignard reagent to the oxygen (methoxide) of the chiral ligand resulting in stereoselective delivery of the organometallic and kinetic control. Such complexation is not possible with a naphthylboronate so the observed low ee is perhaps not surprising. The high ee obtained with tertiary amine phosphine ligand **13** suggests that pre-complexation is arising between nitrogen and boron prior to transmetallation. Use of a bidentate phosphine ligand (**14**) resulted in a decrease in the observed selectivity which is similar to the results obtained with Grignard reagents.[5]

In summary, we have performed the first series of asymmetric Suzuki cross-coupling reactions to prepare chiral binaphthalenes with ee's up to 85%. The reaction permits the use of functional groups which are incompatible with Grignard reagents (the organometallic component used in all previously reported syntheses). The extension of this methodology to other biaryl systems is ongoing in our laboratories.

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