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RESEARCH ARTICLE

Application of a Ferrocene-Based Palladacycle Precatalyst to Enantioselective Aryl-Aryl Kumada Coupling

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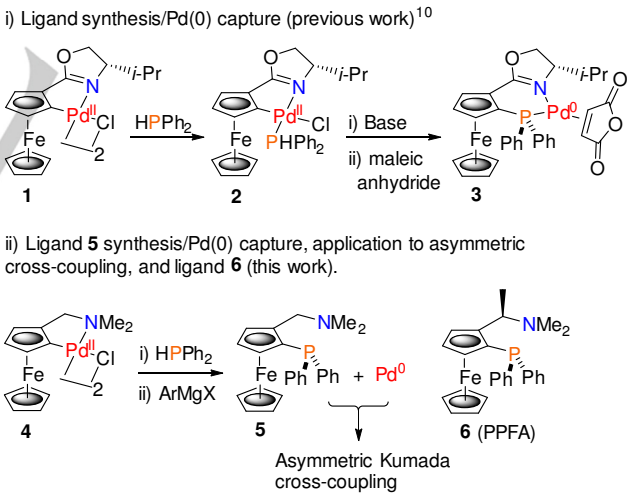
Abstract: The palladium catalysed reaction of 1-iodo-2-methylnaphthalene and 2-methyl-1-naphthylmagnesium bromide gave quantitatively an (S_a)-configured cross-coupled product in 80% e.e. using (R,S_p)-PPFA as a ligand. *N*,*N*-Dimethylaminomethylferrocene was cyclopalladated (Na_2PdCl_4, (*S*)-Ac-Phe-OH, 93% e.e., as determined by ^{1}H NMR as a result of self-induced non-equivalence), and the resulting (S_p)-configured dimeric palladacycle was employed as a precatalyst for this cross-coupling reaction (5 mol%). Addition to the palladacycle of diphenylphosphine and subsequent base-promoted bidentate ligand synthesis and palladium capture gave an *in situ* generated catalyst resulting in an (S_p)-configured product in up to 71% e.e.

Introduction

The importance of cross-coupling reactions to organic synthesis has resulted in the development of numerous palladium catalysed processes for the construction of carbon-carbon and carbon-heteroatom bonds.[1] These reactions generally require the addition of a suitably ligated Pd(0) or Pd(II) complex, the latter requiring *in situ* reduction to Pd(0) prior to catalysis.[2] Examples of Pd(II) precursors include palladacycles which have been used as precatalysts in, for example, the Heck,[3] Suzuki-Miyaura,[4] Sonogashira[5] and Buchwald-Hartwig amination reactions.[6] Asymmetric palladium catalysed cross-coupling reactions have been developed extensively in recent years.[7] Although chiral non-racemic palladacycles and related pincer complexes have been applied widely for the catalytic synthesis of chiral non-racemic compounds,[8] there are seemingly no examples of the successful use of these in enantioselective cross-coupling reactions proceeding *via* a Pd(0)/Pd(II) catalytic cycle.[9]

We reported recently the transformation of planar chiral palladacycle **1**, *via* **2**, into P-N ligated Pd(0) complex **3** by a novel ligand synthesis/palladium capture procedure (Scheme 1).[10] In the absence of maleic anhydride this resulted in an active and enantioselective P-N/Pd(0) catalyst for asymmetric allylic alkylation. In light of these outcomes there are two reasons why palladacycle **4** also has significant potential as a precatalyst for this ligand synthesis/palladium capture procedure. Firstly, it may be synthesised in one step by highly enantioselective palladation from commercially available *N*,*N*-dimethylaminomethylferrocene.[11] Secondly, use in this procedure with diphenylphosphine and a suitable base was anticipated to give planar chiral ligand **5**, closely related to PPFA **6**.[12] This latter ligand has featured extensively in the development of enantioselective cross-coupling procedures, notably: i) nickel and palladium catalysed coupling of secondary alkyl Grignard and organozinc reagents with alkenyl bromides;[13] ii) axial chirality generating palladium catalysed coupling between aryl halides and aryl organometallics [$B(OR)_2$,[14] $B(OH)_2$[15], Zn,[16] and In[17]]. In this paper we describe an aryl Grignard reagent based palladium catalysed Kumada cross-coupling for non-racemic biaryl synthesis, and the successful application of palladacycle (S_p)-**4** as a precatalyst for this reaction.

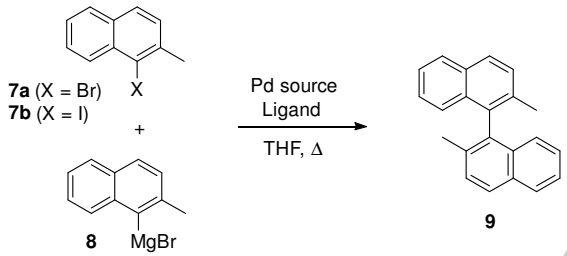


Scheme 1. Palladacycles for ligand synthesis and palladium capture procedures.

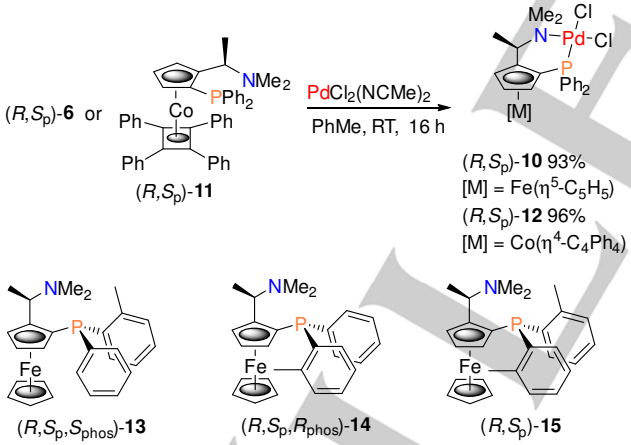
Results and Discussion

Previous attempts at Kumada cross-coupling for the synthesis of chiral non-racemic biaryls have resulted in low enantioselectivity,[18] although nickel catalysis with a PPFA related ligand (NMe_2 replaced by OMe) has proven successful (up to 95% e.e.).[19] To reinvestigate palladium catalysis the cross-coupling between 1-halo-2-methylnaphthalenes **7a**/**b** and 2-methyl-1-naphthylmagnesium bromide **8** was used as a model reaction

(Scheme 2). Our aim was to establish the viability of using PPFA as a ligand for this reaction prior to investigating the use of palladacycle **4** as a precatalyst. Initial racemic cross-coupling with 2.5 mol% of $Pd(PPh_3)_2Cl_2$ and bromide **7a** was partially successful (Table 1, entry 1), but under the same conditions (THF, 70 °C, 24 h) iodide **7b** gave complete conversion (entry 2). As $PdCl_2$ is insoluble in THF, the PPFA catalyst precursor (R,S_p)-**10** was prepared essentially as previously reported (Scheme 3).[13b] Utilisation of 5 mol% of (R,S_p)-**10** in the cross-coupling procedure run over 48 hours at 70 °C resulted in a modest 38% conversion (entry 3). Doubling both the reaction time and the number of equivalents of Grignard reagent (to 2 equiv.) resulted in a quantitative conversion (entry 4). Significantly, the use of the (R,S_p)-PPFA based catalyst in both of these runs gave (S_a)-**9** in 80% e.e. This level of enantioselectivity is similar to that reported previously from the use of PPFA in related palladium catalysed cross-couplings, and the sense of enantioselectivity is the same.[14-17] The 5 mol% catalyst loading is generally much less than that used in these previous examples.



Scheme 2. Palladium catalysed Kumada cross-coupling.



Scheme 3. Palladium complexes (R,S_p)-**10** and (R,S_p)-**12**, and additional ligands (R,S_p,S_{phos})-**13**, (R,S_p,R_{phos})-**14** and (R,S_p)-**15**.

As an alternative to using preformed PPFA/Pd(II) complex **10**, a Pd(0) source was also investigated by use of THF soluble $Pd_2(dba)_3$. Use of 5 mol% with 10 mol% (R,S_p)-**6** for 24 h was partially successful (entry 5), with higher conversions resulting on prolonging the reaction time to 48 and then 72 hours (entries 6 and 7). Complete conversion to (S)-**9** in 78% e.e. was achieved on increasing the temperature to 80 °C (entry 8) and the reaction was shown to be complete after 24 h with no reduction in e.e. (entry 9).

Table 1. Synthesis of **9** by palladium catalysed Kumada cross-coupling with conventional methods of catalyst generation.[a]

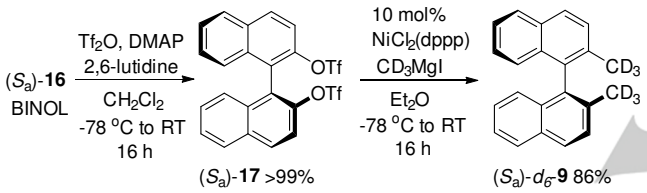
Entry	Pd source (mol%)	Ligand (mol%)	Temp (time)	Conversion (%)	e.e.[b] (%)
1[c,d]	$Pd(PPh_3)Cl_2$ (2.5)	-	70 °C (24 h)	47	-
2[d]	$Pd(PPh_3)Cl_2$ (2.5)	-	70 °C (24 h)	100	-
3[d]	(R,S_p)-**10** (5)	-	70 °C (48 h)	38	80
4[e]	(R,S_p)-**10** (5)	-	70 °C (96 h)	100	80
5[f]	$Pd_2(dba)_3$ (5)	(R,S_p)-**6** (10)	70 °C (24h)	39	72
6[f]	$Pd_2(dba)_3$ (5)	(R,S_p)-**6** (10)	70 °C (48 h)	45	75
7[f]	$Pd_2(dba)_3$ (5)	(R,S_p)-**6** (10)	70 °C (72 h)	49	77
8[f]	$Pd_2(dba)_3$ (5)	(R,S_p)-**6** (10)	80 °C (72 h)	100	78
9[f]	$Pd_2(dba)_3$ (5)	(R,S_p)-**6** (10)	80 °C (24 h)	100	78
10[f]	$Pd_2(dba)_3$ (5)	(R,S_p)-**11** (10)	80 °C (72 h)	89	38
11[e]	(R,S_p)-**12** (5)	-	70 °C (96 h)	11	0
12[f]	$Pd_2(dba)_3$ (5)	(R,S_p,S_{phos})-**13** (10)	80 °C (72 h)	93	45
13[f]	$Pd_2(dba)_3$ (5)	(R,S_p,R_{phos})-**14** (10)	80 °C (72 h)	67	76
14[f]	$Pd_2(dba)_3$ (5)	(R,S_p)-**15** (10)	80 °C (72 h)	93	63
15[f,g]	$Pd_2(dba)_3$ (5)	(R,S_p)-**6** (10)	80 °C (72 h)	82[h]	80[h]

[a] Reaction of **7b** with **8** unless otherwise stated (0.13 M of **7b**, sealed tube). [b] Of (S_a)-**9** as determined by chiral HPLC. [c] **7a** as starting material. [d] 1 equiv of **8**. [e] 2 equiv of **8**. [f] 1.5 equiv of **8**. [g] With 50 mol% (S_a)-d_6-**9**. [h] Of (S_a)-**9**.

Ligands related to PPFA were also investigated. The η^4-tetraphenylcyclobutadiene-cobalt analogue (PPCA) (R,S_p)-**11** (Scheme 3),[20] either with $Pd_2(dba)_3$ (entry 10), or as a preformed palladium complex (R,S_p)-**12** (entry 11), only resulted in appreciable conversion in the former case, and with a significantly reduced e.e. Addition of a chirality element to an existing chiral non-racemic ligand often results in an increase in catalysis product e.e. for one of the two resulting diastereoisomers.[21] To this end, we tested the *P*-stereogenic PPFA derivatives (R,S_p,S_{phos})-**13** and (R,S_p,R_{phos})-**14** containing an *ortho*-tolyl group in place of one or other of the diastereotopic phosphorus phenyl substituents.[22] In this instance, the matched (R,S_p,R_{phos}) diastereoisomer resulted in a product e.e. value very similar to that obtained from the parent PPFA ligand **6**. It is of note that compared to the di-*ortho*-tolyl ligand (R,S_p)-**15**, there is a clear

increase and decrease in product e.e. on creation of a *P*-stereogenic centre by methyl group removal (entries 12-14). This, and the results obtained with (R,S_p)-**11**, reveals the sensitivity of these ligands to steric influences with respect to application in this asymmetric cross-coupling procedure.

A feature of the optimisation study with $Pd_2(dba)_3$ as palladium source was an increase in product e.e. with increased conversion (from 72 to 77% e.e., entries 5-7). To test if the enantioenriched cross-coupling product was influencing beneficially the stereoselectivity of this reaction, we first synthesised deuterated (S_a)-d_6-**9**. This was achieved by quantitative conversion of (S_a)-BINOL **16** into bis-triflate (S_a)-**17**, followed by nickel catalysed cross-coupling with methyl-d_3-magnesium iodide (Scheme 4). Complete methyl deuteration in the product was confirmed by ^{1}H NMR spectroscopy, with the e.e. determined as >99% by chiral HPLC [(S_a)-d_6-**9**/(S_a)-**9** having identical retention times]. Subsequent Kumada cross-coupling in the presence of 50 mol% (S_a)-d_6-**9** resulted in a product containing 38% of this deuterated material with an e.e. of 88%, corresponding to an e.e. of 81% for non-deuterated (S_a)-**9** (entry 15). Therefore any influence from the product on the reaction enantioselectivity is very small.



Scheme 4. Synthesis of (S_a)-d_6-**9**.

Following the successful use of PPFA **6** as a ligand in this cross-coupling procedure, we next investigated the use of palladacycle (S_p)-**4** as a precatalyst for this reaction. The palladacycle was synthesised from **18** as reported previously (Scheme 5).[11b] The absolute configuration of (S_p)-**4** was confirmed by an X-ray crystal structure determination,[23] this also revealing that this exists in the *trans* dimer form in the solid state (Figure 1). For *rac*-**4**[24] the ^{1}H NMR spectrum ($CDCl_3$) contains eight methyl singlets of approximately equal intensity resulting from a 1 : 1 ratio of *cis* and *trans* dimers, each present as a 1 : 1 mixture of (R_p*,R_p*) and (R_p*,S_p*) isomers, with each containing diastereotopic methyl groups (Figure 2a, 3.10 – 2.80 ppm). In contrast, the spectrum of (S_p)-**4** contains four major and four minor methyl singlets in a 14 : 1 ratio (Figure 2b), the major signals arising from an equal mixture of *cis* and *trans* (S_p,S_p) dimers. From this, by application of the Horeau principle, the e.e. is estimated as 93%.[25,26] This example differs from several others where the e.e. was determined by ^{1}H NMR utilising self-induced non-equivalence.[27] In these cases rapid dimerisation exchange on the NMR time-scale gives two sets of signals for a non-racemic mixture of relative intensity equal to the enantiomeric ratio.[28]

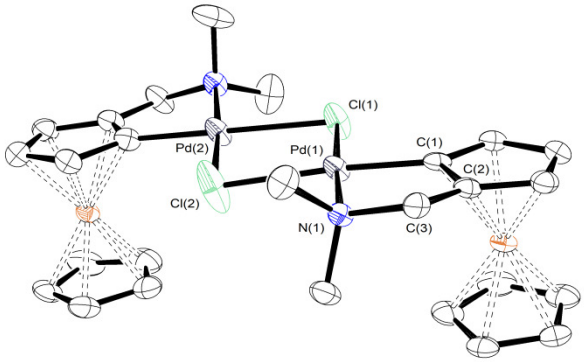


Figure 1. X-ray structure of (S_p)-**4** (hydrogen atoms and solvent of crystallisation omitted for clarity). Thermal ellipsoids are drawn at the 50% probability level. Principal bond lengths [Å] include: C(1)-Pd(1) 1.953(5), N(1)-Pd(1) 2.099(3), Cl(1)-Pd(1) 2.3250(11), Cl(2)-Pd(1) 2.4516(14). Principal bond angles [°] include: C(1)-Pd(1)-N(1) 83.82(15), Cl(1)-Pd(1)-Cl(2) 87.52(4). Principal torsion angles [°] include: C(1)-C(2)-C(3)-N(1) 19.7(5), N(1)-Pd(1)---Pd(2)-N(2) 168.6. Absolute structure parameter = -0.010(10).

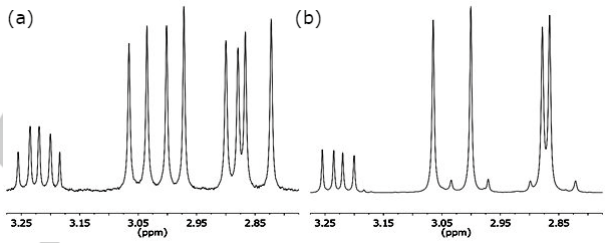
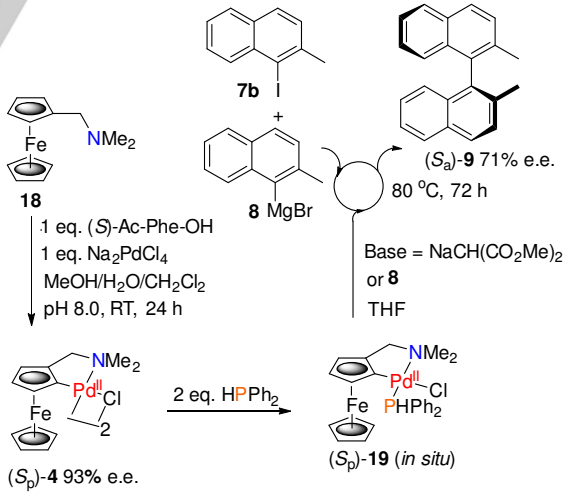


Figure 2. Determination of e.e. by self-induced non-equivalence. Partial ^{1}H NMR spectra of (a) *rac*-**4** and (b) (S_p)-**4**.



Scheme 5. Asymmetric synthesis of (S_p)-**4**, application to ligand synthesis/palladium capture, and the synthesis of (S_a)-**9** by Kumada cross-coupling.

Dimeric palladacycle (S_p)-**4** was dissolved in THF and the phosphine complex (S_p)-**19** formed *in situ* following the addition of two equivalents of diphenylphosphine. In our previous work sodium dimethyl malonate was used to deprotonate the coordinated phosphine **2** and promote C-P bond formation by

reductive elimination.[10] Therefore, after the addition of aryl iodide **7b**, 10 mol% of this base was added followed (after five minutes) by the Grignard reagent **8** and the mixture heated at 80 °C for 72 hours. This resulted in a quantitative conversion to (S_a)-**9** formed in 71% e.e. (Table 2, entry 1). That the Grignard reagent is itself a suitable base was revealed by repeating the reaction in the absence of sodium dimethyl malonate, this resulted in 83% conversion and a slight reduction in selectivity to 68% e.e. (entry 2). Taking into account the 93% e.e. of the starting palladacycle, this corresponds to an (S_a)-**9**/(R_a)-**9** cross-coupling selectivity of up to 76% e.e.,[29] *i.e.* very similar to that obtained with (R,S_p)-**6**. These outcomes reveal the dominance of the element of planar chirality over the selectivity of the reaction.[30] In the absence of added phosphine some cross-coupling took place but the product was essentially racemic (entry 3).

Table 2. Synthesis of **9** by palladium catalysed Kumada cross-coupling with precatalyst (S_p)-**4**.[a]

Entry	$HPPh_2$ (mol%)	Base	Conversion (%)	e.e.[b] (%)
1	10	$NaCH(CO_2Me)_2$[c]	100	71
2	10	**8**	83	68
3	0	**8**	48	<1

[a] Reaction of **7b** with 1.5 eq. **8** with 5 mol% (S_p)-**4**, THF, 80 °C, 72 h (0.13 M of **7b**, sealed tube). [b] Of (S_a)-**9** as determined by chiral HPLC. [c] 10 mol%.

In our previous study we were able to isolate and characterise the monomeric diphenylphosphine adduct **2**, and in turn, follow by NMR spectroscopy the conversion of this into the maleic anhydride coordinated ligand synthesis/palladium capture complex **3** (Scheme 1, i). In contrast, attempts to characterise the adduct **16** resulting from the addition of diphenylphosphine to (S_p)-**4** were not successful, suggesting that this is significantly more reactive. That this leads, at least in part, to an (S_p)-**5**/palladium capture catalyst is supported by the close similarity, with respect to activity, enantioselectivity and absolute configuration, of the outcome of asymmetric Kumada cross-coupling when compared to the use of closely related ligand (R,S_p)-**6**.

Conclusion

We have established that the palladium catalysed aryl-aryl Kumada coupling of 1-iodo-2-methylnaphthalene and 2-methyl-1-naphthylmagnesium bromide is a viable protocol using PPFA as a ligand (up to 80% e.e.). This outcome led to the successful application of palladacycle (S_p)-**4** as a precatalyst for this reaction on combination with diphenylphosphine in a ligand synthesis/palladium capture process (up to 71% e.e.). As (S_p)-**4** may be obtained from readily available *N,N*-dimethylaminomethylferrocene by enantioselective palladation, this overall protocol generates the catalyst efficiently in just two steps.

Experimental Section

General Procedure for the preparation of 9 by Kumada Coupling with $Pd_2(dba)_3$. Tris(dibenzylideneacetone)dipalladium(0) (0.0115 g, 0.0125 mmol) and ligand (0.025 mmol) were added to a flame dried Schlenk tube, dissolved in THF (0.5 mL), and stirred for 30 mins resulting in a colour change from deep purple to deep orange. To this was added **7b** (0.04 mL, 0.25 mmol) and the reaction stirred for 10 mins resulting in a colour change to deep yellow. 2-Methyl-1-naphthylmagnesium bromide **8** solution (0.25 M) (1.5 mL, 0.38 mmol) was then added and the mixture stirred for 5 mins causing the colour to change back to deep orange. The reaction was then heated with stirring at 80 °C for 72 h. After cooling the reaction was quenched with saturated ammonium chloride, separated with diethyl ether, and the organic phase dried ($MgSO_4$) and the solvent removed *in vacuo*. A ^{1}H NMR was performed at this point to determine the conversion. Purification by column chromatography (SiO_2, 100% hexane) gave **9** as a colourless tacky solid. The e.e. was determined by HPLC using a CHIRALCEL OD-H column; eluent = 100% hexane; flow rate = 0.5 mL min^{-1}; concentration = 6 µM, injection volume = 5 µl, wavelength = 254 nm. (S_a)-enantiomer RT = 19.42 min, (R_a)-enantiomer RT = 24.82 min. ^{1}H NMR (500 MHz, $CDCl_3$) 7.88 (4H, t, J = 8.0 Hz, Ar*H*), 7.51 (2H, d, J = 8.4 Hz, Ar*H*), 7.39 (2H, ddd, J = 8.1, 6.8, 1.1 Hz, Ar*H*), 7.20 (2H, ddd, J = 8.2, 6.8, 1.3 Hz, Ar*H*), 7.04 (2H, d, J = 8.4 Hz, Ar*H*), 2.03 (6H, s, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) 135.3 (Ar*C*), 134.4 (Ar*C*), 132.9 (Ar*C*), 132.4 (Ar*C*), 128.9 (Ar*C*), 128.1 (Ar*C*), 127.6 (Ar*C*), 126.2 (Ar*C*), 125.8 (Ar*C*), 125.0 (Ar*C*), 20.2 (*C*H$_3$). Matches previously reported data.[19]

Procedure for the preparation of 9 by Kumada Coupling with palladacycle (S_p)-4. In a flame dried Schlenk tube (tube 1), sodium *tert*-butoxide solution (2 M in THF) (0.0125 mL, 0.025 mmol) was added to a solution of dimethyl malonate (5.7 µL, 0.05 mmol) in THF (0.5 mL) at 0 °C. After stirring for 30 mins the solvent was removed under high vacuum to give a beige residue. In a separate flame dried Schlenk tube (tube 2), (S_p)-**4** (0.0096 g, 0.0125 mmol) was dissolved in THF (0.5 mL) and diphenylphosphine (4.35 µL, 0.025 mmol) was added and the mixture stirred for 5 mins. To this was then added **7b** (0.064 g, 0.25 mmol) and the solution stirred for 10 mins. The contents of Schlenk tube 2 were transferred to Schlenk tube 1 and stirred for 5 mins, after which 2-methyl-1-naphthylmagnesium bromide **8** solution (0.25 M) (1.5 mL, 0.375 mmol) was added and the reaction mixture stirred at room temperature for 5 mins before heating with stirring at 80 °C for 72 h. After cooling the reaction was quenched with saturated ammonium chloride, separated with diethyl ether, and the organic phase dried ($MgSO_4$) and the solvent removed *in vacuo*. A ^{1}H NMR was performed at this point to determine the conversion. Purification by column chromatography (SiO_2, 100% hexane) gave **9** as a colourless tacky solid. The e.e. was determined as described above.

Acknowledgements

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Keywords: cross-coupling • enantioselective • ferrocene • ligand • palladacycle

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[23] Deposition Number 1982092 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.
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[25] Where d.r. = $[1 + (e.e.)^2]/[1-(e.e.)^2]$. See: J. P. Vigneron, M. Dhaenea, A. Horeau, *Tetrahedron* **1973**, *29*, 1055-1059.
[26] This is in good agreement with the 95% e.e. reported previously for the product of this enantioselective cyclopalladation.[11b]
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[28] For these examples the racemate gives a single set of signals as the weighted average of the signals for the *R*, *R*,*S* and *R*,*R* monomer and dimers is equal to that for the *S*, *R*,*S* and *S*,S monomer and dimers. For a non-racemic mixture the equilibrium proportion of *R*/*R*,*S*/*R*,*R* ≠ *S*/*R*,*S*/*S*,*S* and two sets of peaks can arise.
[29] Assuming a linear relationship between e.e. (S_p)-**4** and e.e. (S_a)-**9**.
[30] A previous comparison between ligands (S_p)-**4** and (R,S_p)-**5** in palladium catalysed coupling of secondary alkyl Grignard reagents with alkenyl bromides also noted the dominance of the element of planar chirality. See reference 13b.

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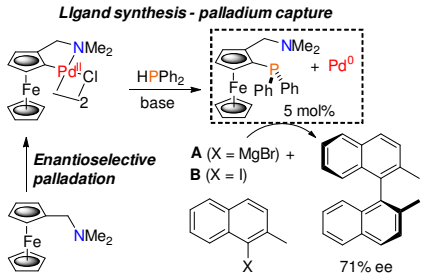

Ligand synthesis/palladium capture was utilised to generate *in situ* a catalyst for enantioselective aryl-aryl Kumada Coupling. The palladacycle employed was synthesised by highly enantioselective palladation, providing an efficient overall two-step catalyst generation procedure for application in asymmetric synthesis.