Ferrocenyloxazoline Derived Planar Chiral Palladacycles: C-H Activation, Transmetalation and Reversal of Diastereoselectivity

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ABSTRACT: Reinvestigation of the palladation of (*S*)-2-ferrocenyl-4-(methylethyl)oxazoline with $Pd(OAc)_2$ in CH_2Cl_2 was found to proceed with a dr of 3.6 : 1 in favour of the resulting (S,S_p)-palladacycle. A similar 4 : 1 dr was obtained using Na_2PdCl_4 in MeOH. As an alternative approach, highly diastereoselective lithiation (dr >100 : 1) and transmetalation was investigated. Addition of $PdX_2(COD)$ (X = Cl, Br) to (S,R_p)-2-lithio-1-(2'-(4'-methylethyl)oxazolinyl)ferrocene resulted in double halide substitution and formation of *cis*-(S,S,S_p,S_p)-*bis*-[2-(2'-(4'-methylethyl)oxazolinyl)ferrocene, 1-*C*, 3'-*N*]palladium(II) (42% from X = Cl, 50% from X = Br). Selective mono proto-depalladation with HCl gave an (S,S_p)-palladacycle containing a removable ferrocenyloxazoline ligand. Addition of $PdCl_2(MeCN)_2$ to mercuracycles in acetonitrile, themselves generated from Li-Hg transmetalation, followed by a brine wash gave (S,S_p)-di-μ-chlorobis[2-(2'-(4'-methylethyl)oxazolinyl)ferrocene, 1-*C*, 3'-*N*]dipalladium(II) as a single diastereoisomer in high yield. The alternative (S,R_p)-diastereoisomer was obtained in the same way by use of a deuterium blocking group to reverse lithiation diastereoselectivity.

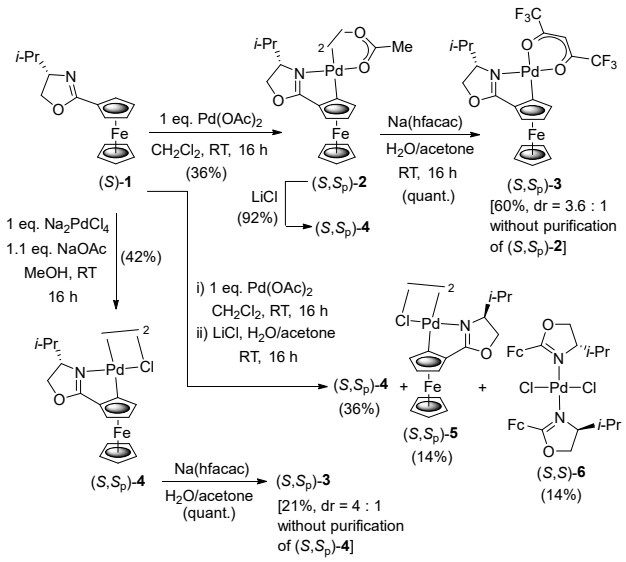
INTRODUCTION

The synthesis and application of palladacycles is a significant branch of organometallic chemistry.[1] In addition to the use of these compounds in the development of new materials,[2] they have also be employed as pre-catalysts[3] and catalysts[4] in organic synthesis. Palladacycles have also been identified as intermediates in many palladium-catalysed C-H activation reactions resulting in new C-C[5] or C-heteroatom bonds.[5b,6] Similarly, C-H activation is also the principle method used for palladacycle synthesis.[7] This may be accompanied by the generation of a new element of chirality in an enantioselective[8] or diastereoselective[9] process that typically, but not exclusively,[10] results in a planar-chiral product. Ferrocenyloxazolines, such as (*S*)-valine derived (*S*)-**1**, are readily synthesised precursors to planar chiral derivatives that result from the addition of an electrophile after highly diastereoselective α-lithiation.[11] Introduction in this way of iodine, followed by oxidative addition of Pd(0), provides access to planar chiral palladacycles.[12] Alternatively, the direct cyclopalladation of (*S*)-**1** is known as a route to (S,S_p)-palladacycles, although the diastereoselectivity of this reaction is not clear.[9d] In view of the potential of palladacycles derived from (*S*)-**1** as catalysts and precatalysts in asymmetric synthesis we chose to reinvestigate this C-H activation reaction. We also explored transmetalation approaches to the selective generation of both planar chiral palladacycle diastereoisomers. The results of these investigations are reported in this paper.

RESULTS AND DISSCUSION

The cyclopalladation of (*S*)-**1** with $Pd(OAc)_2$ in CH_2Cl_2 heated at reflux was performed as previously reported.[9d] In our hands (S,S_p)-**2** was obtained in 12% yield as a single diastereoisomer following chromatography of the initially very dark product mixture and subsequent crystallisation from CH_2Cl_2/hexane (Scheme 1). Performing the reaction at room temperature resulted in a less dark product mixture and an increase in the yield of the pure diastereoisomer to 36%. Use of glacial acetic acid at 95 °C with $Pd(OAc)_2$ resulted only in decomposition.[9b] The isolation of (S,S_p)-**2** as a single diastereoisomer following crystallization was supported by formation of the hfacac complex (S,S_p)-**3** which showed a single set of signals by ^{19}F NMR spectroscopy at -74.72 and -75.71 ppm. Crystals of (S,S_p)-**3** obtained from EtOAc/hexane confirmed the stereochemical assignment (Figure 1). The diastereoselectivity of the room temperature cyclopalladation of (*S*)-**1** was determined as 3.6 : 1 by forming the hfacac complex from the product mixture prior to purification. This gave an additional set of ^{19}F signals at -74.73 and -75.68 ppm. The improved 60% yield for this reaction confirmed the poor stability of (S,S_p)-**2** towards column chromatography. This was required to remove impurities from the initially very dark product mixture prior to crystallisation to give diastereomerically pure (S,S_p)-**2**.

Scheme 1. Cyclopalladation of oxazoline (*S*)-**1** and subsequent ligand exchange.



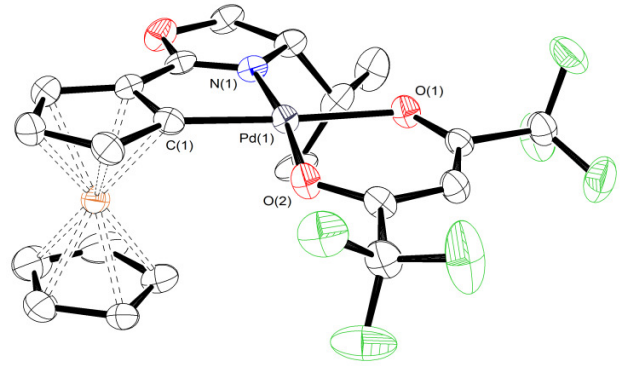


Figure 1. X-ray structure of (*S*,*S*p)-**3**. Hydrogens omitted for clarity. Structure depicted is one of four molecules contained in the unit cell. Principal bond lengths [Å] include: C(1)-Pd(1) 1.955(4), N(1)-Pd(1) 2.025(3), O(1)-Pd(1) 2.099(3), O(2)-Pd(1) 2.025(3). Principal bond angles [°] include: C(1)-Pd(1)-N(1) 80.87(14), O(1)-Pd(1)-O(2) 92.40(10). Thermal ellipsoids are drawn at the 50% probability level. Flack parameter = -0.007(5).

We next investigated the cyclopalladation of (*S*)-**1** using Na_2PdCl_4 in methanol at room temperature. The chloride bridged palladacycle (*S*,*S*p)-**4** was obtained in 42% yield as a single diastereoisomer after chromatography. In contrast to (*S*,*S*p)-**2**, its chloride-bridged congener (*S*,*S*p)-**4** resulted in less decomposition during column chromatography. Crystals of (*S*,*S*p)-**4** suitable for X-ray crystallography were obtained from CH_2Cl_2/hexane showing that in this phase the dimer (*S*,*S*p)-**4** is in the *trans* configuration (Figure 2 - with t*rans* referring to the opposite orientation of the bidentate CN ligands about the Pd_2Cl_2 core). In contrast, examination of these crystals by ^{1}H NMR spectroscopy in $CDCl_3$ revealed a 1.7 : 1 ratio of isomers, although the identity of the major dimer as *cis* or *trans* could not be determined.

The configuration of (*S*,*S*p)-**4** was further confirmed by generating this complex by ligand exchange from (*S*,*S*p)-**2** on reaction with LiCl in H_2O/acetone. Additionally, reaction of Na(hfacac) with (*S*,*S*p)-**4**, gave (*S*,*S*p)-**3** in a quantitative yield. The selectivity of the cyclopalladation reaction with Na_2PdCl_4 was determined by omitting the chromatography step prior to reaction with Na(hfacac), and this gave a 4 : 1 mixture of diastereoisomers. The chloride bridged palladacycle (*S*,*S*p)-**4** was also obtained after room temperature palladation with $Pd(OAc)_2$, acetate/chloride ligand exchange, and subsequent column chromatography. In addition to (*S*,*S*p)-**4** (36%), and its diastereoisomer (*S*,*R*p)-**5** (14%), this method also gave the oxazoline coordinated palladium chloride adduct (*S*,*S*)-**6** (14%). Lower yields of (*S*,*S*p)-**4** (22%) and (*S*,*R*p)-**5** (10%) were obtained when the initial cyclopalladation step with $Pd(OAc)_2$ was carried out at 40 °C, as a result of cyclopalladation product decomposition under these conditions. Analysis of (*S*,*S*)-**6** by X-ray crystallography revealed two rotameric structures in the unit cell (Figure 3), these being also present in solution in a 1 : 1 ratio, as determined by ^{1}H NMR spectroscopy in MeCN-d^3.

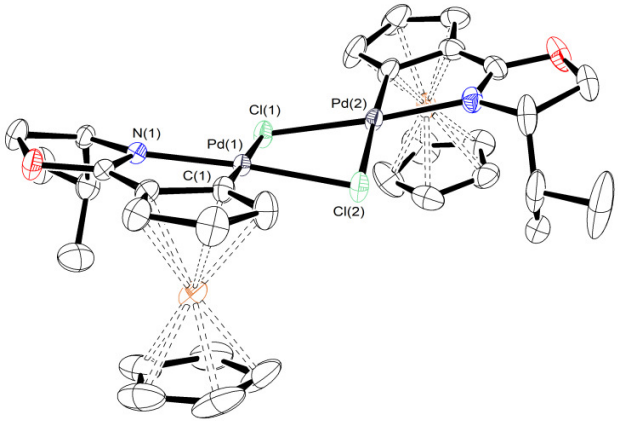


Figure 2. X-ray structure of (*S*,*S*p)-**4**. Hydrogens omitted for clarity. Principal bond lengths [Å] include: C(1)-Pd(1) 1.948(3), N(1)-Pd(1) 2.048(2), Cl(1)-Pd(1) 2.4636(8), Cl(2)-Pd(1) 2.3130(7). Principal bond angles [°] include: C(1)-Pd(1)-N(1) 80.27(11), Cl(1)-Pd(1)-Cl(2) 88.56(2). Principal torsion angle [°]: C(1)-Pd(1)-Cl(2)-Pd(2) -160.20. Thermal ellipsoids are drawn at the 50% probability level. Flack parameter = -0.005(6).

In light of the modest diastereoselectivity of direct cyclopalladation, and the relatively low yields obtained after purification, we chose to explore an alternative transmetalation approach following initial highly diastereoselective lithiation.[13] This was achieved by the addition of *s*-BuLi to (*S*)-**1** in diethyl ether in the presence of TMEDA (Scheme 2).[11a] Subsequent addition of a solution of $PdBr_2$(COD) in THF at 0 °C , and warming to room temperature, resulted in lithium-palladium transmetalation occurring twice and formation of complex (*S*,*S*,*S*p,*S*p)-**7** in 50% yield. The same product was obtained in 42% yield using the same procedure with $PdCl_2$(COD). Crystals of complex (*S*,*S*,*S*p,*S*p)-**7** were obtained from a concentrated sample in chloroform and the *cis* configuration determined by X-ray crystallog-

raphy (Figure 4). The *cis* configuration is, at least in part, a consequence of the S,S_p configured ligands, as the alternative *trans* arrangement would result in an steric clash between the *iso*-propyl and iron-cyclopentadienyl moieties.

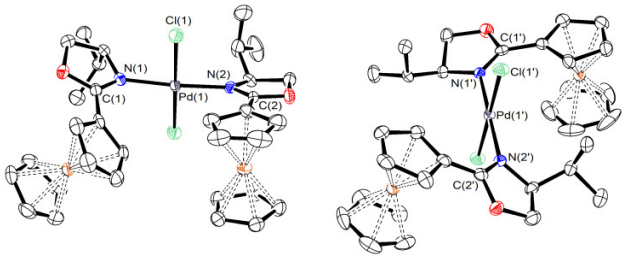
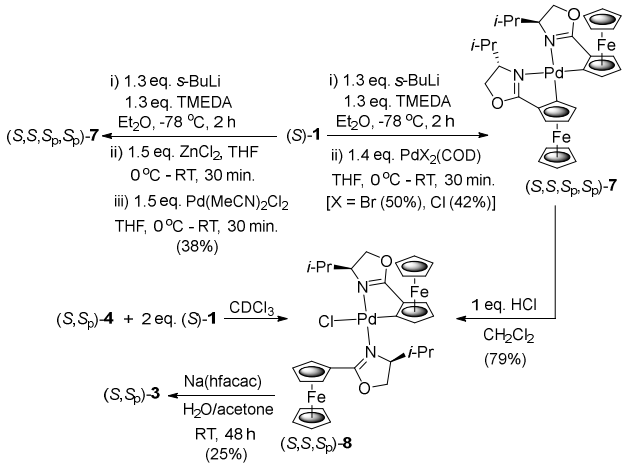


Figure 3. X-ray structures of (*S*,*S*)-**6**. Hydrogens omitted for clarity. Principal torsion angles [°] include: Cl(1)-Pd(1)-N(1)-C(1) -79.48, Cl(1)-Pd(1)-N(2)-C(2) 69.43, Cl(1')-Pd(1')-N(1')-C(1') 67.55, Cl(1')-Pd(1')-N(2')-C(2') 74.22. Thermal ellipsoids are drawn at the 50% probability level. Flack parameter = -0.003(9).

Scheme 2. Use of lithium-palladium transmetalation for the synthesis of palladacycles derived from (*S*)-**1**.



In an attempt to add selectively a single ferrocenyloxazoline unit to palladium, zinc chloride was added to the reaction after diastereoselective lithiation to generate, by transmetalation, the corresponding ferrocenylzinc intermediate. We reasoned that its lower reactivity would reduce the likelihood of double addition, but instead after addition of $PdCl_2(MeCN)_2$ only (S,S,S_p,S_p)-**7** was again isolated. The absence from these reactions of any evidence for the formation of (S,S_p)-**4** suggests that the second M to Pd (M = Li or Zn) transmetalation reaction is faster than the first, an outcome consistent with the high *trans*-effect of the anionic ferrocenyl anion ligand.[14]

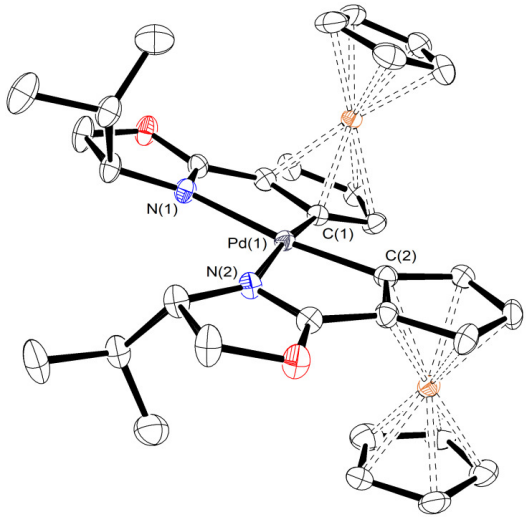


Figure 4. X-ray structure of (S,S,S_p,S_p)-**7**. Hydrogens omitted for clarity. Structure depicted is one of two molecules contained in the unit cell. Principal bond lengths [Å] include: C(1)-Pd(1) 1.995(6), N(1)-Pd(1) 2.148(4). Principal bond angles [°] include: C(1)-Pd(1)-N(1) 81.09(19), C(1)-Pd(1)-C(2) 95.8(3), N(1)-Pd(1)-N(2) 102.5(2). Thermal ellipsoids are drawn at the 50% probability level. Flack parameter = -0.021(9).

Addition of one equivalent of 2M HCl in Et_2O to a solution of (S,S,S_p,S_p)-**7** in dichloromethane resulted in mono proto-depalladation and formation of palladacycle (S,S,S_p)-**8** (Scheme 2). Mono proto-depalladation also took place when (S,S,S_p,S_p)-**7** was added to biphasic 1.6M $HCl_{(aq)}$/dichloromethane. After shaking, separation and evaporation gave (S,S,S_p)-**8**. The identity of this complex was confirmed by the addition of two equivalents of (*S*)-**1** to one equivalent of (S,S_p)-**4** in an NMR tube, confirming that oxazoline addition to the chloride-bridged dimer is essentially irreversible. The oxazoline ligand could be removed partially by reaction with Na(hfacac) over a 48 hour period, giving a conversion of 60% and an isolated 25% yield of (S,S_p)-**3**. Thus overall, lithium-palladium transmetalation is a viable route to planar chiral palladacycles, albeit that the initially formed bispalladacycle requires subsequent proto-demetalation and ligand exchange to generate non-palladacycle/ferrocenyloxazoline based coordination sites.

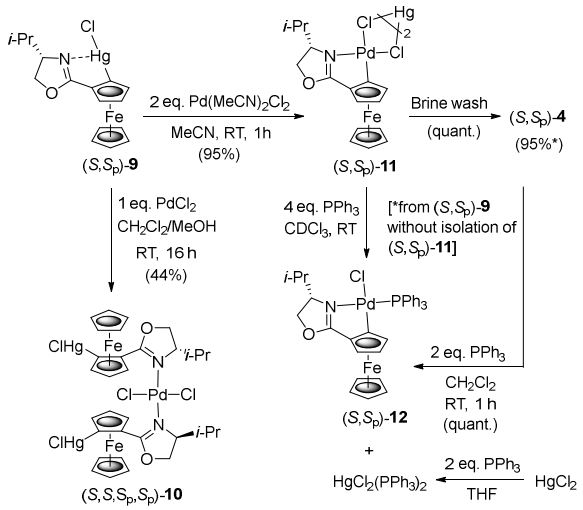
We recently reported the synthesis of planar chiral iridacycles by transmetalation with mercury substituted planar chiral ferrocenyloxazolines.[15] One benefit of this route is that the stable mercury species can be synthesised and where needed purified to give a single diastereoisomer, leading in turn to a single diastereoisomer of transmetalation product. With this in mind we first attempted the synthesis of (S,S_p)-**4** utilizing this methodology. Mercuracycle (S,S_p)-**9** was synthesised as reported previously with an improved yield of 73% (see supporting information). This was then used in conjunction with $PdCl_2(MeCN)_2$ under different conditions in the attempted synthesis of (S,S_p)-**4** (Table 1 – see supporting information for a full list of palladium sources and conditions investigated).

Table 1. Towards the synthesis of (S,S_p)-4 by transmetalation with (S,S_p)-9.

Entry	Solvent	Temperature (°C)	Major Product (yield)[a]
1	CH_2Cl_2	40	(S,S,S_p,S_p)-**10**[b]
2	Acetone	56	(S,S_p)-**4** (48%)[b]
3	MeCN	60	(S,S,S_p,S_p)-**10**[b]
4	Acetone[c]	56	(S,S,S_p,S_p)-**10**
5	Acetone[d]	rt	(S,S_p)-**11**[b,e]
6	MeCN[d,f]	rt	(S,S_p)-**11** (95%)
7	MeCN[d,f,g]	rt	(S,S_p)-**4** (95%)

All reactions were carried out with 1 eq. of $PdCl_2(MeCN)_2$ with a reaction time of 16 hours unless otherwise stated. [a]Yield of (S,S,S_p,S_p)-**10** not determined. [b]Formation of Pd black observed. [c]Addition of 10 eq. of TBAC. [d]Reaction time reduced to 1 hour. [e]Yield not determined. [f]2 eq. of $PdCl_2(MeCN)_2$ used. [g]Reaction followed immediately by a brine wash.

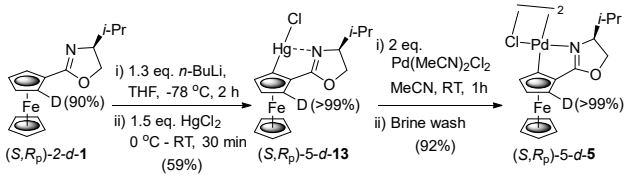
Scheme 3. Transmetalation products utilising (S,S_p)-9.



An initial series of reactions with CH_2Cl_2, acetone or MeCN as solvent heated at reflux resulted in palladium black formation (entries 1-3). The desired palladacycle (S,S_p)-**4** was obtained as a single diastereoisomer in 48% yield in acetone (entry 2), the other reactions resulting only in adduct (S,S,S_p,S_p)-**10** (Scheme 3). The identity of (S,S,S_p,S_p)-**10** was revealed initially by the similarity of its ^{1}H NMR spectrum to that of (S,S)-**6**, in particular by both complexes displaying signals corresponding to a 1 : 1 ratio of rotamers. Furthermore, (S,S,S_p,S_p)-**10** was prepared with a yield of 44% by addition of $PdCl_2$ to a solution of (S,S_p)-**9** in 3 : 2 CH_2Cl_2/MeOH. Repetition of the acetone based reaction with addition of TBAC (tetrabutylammonium chloride) prevented palladium black formation but only resulted in adduct (S,S,S_p,S_p)-**10** (entry 4). In contrast, performing this reaction in the absence of TBAC at room temperature (*ca.* 22 °C) still resulted in significant darkening of the reaction, but a new complex was formed as the major product. For this, a cyclopentadienyl singlet at 4.38 ppm in the ^{1}H NMR spectrum, and three multiplets at 4.64, 4.55 and 4.12 ppm resulting from a doubly substituted cyclopentadienyl ring, were similar to but different from the other palladacycles described in this work. Addition to this species of four equivalents of PPh_3 revealed only two peaks (1 : 1 ratio) in the ^{31}P NMR spectrum of the resulting product at 38.03 and 27.69 ppm. These two signals were identified as the phosphine complexes (S,S_p)-**12** and $HgCl_2(PPh_3)_2$ by their separate preparation from palladacycle (S,S_p)-**4** and $HgCl_2$ respectively. In light of this stoichiometry we tentatively assigned the identity of this precursor complex as palladacycle (S,S_p)-**11** containing a bridging mercury moiety.[16]

Changing to acetonitrile as solvent at room temperature resulted in the complete loss of mercuracycle (S,S_p)-**9** and immediate formation of (S,S,S_p,S_p)-**10** and (S,S_p)-**11**. Increasing to two the number of equivalents of $Pd(MeCN)_2Cl_2$ employed resulted in the sole formation of (S,S_p)-**11** which was isolated in 95% yield (entry 6). Washing a CH_2Cl_2 solution of (S,S_p)-**11** with brine gave cleanly the palladacycle (S,S_p)-**4**. Finally, use of the same conditions followed by a brine wash immediately before silica filtration gave desired palladacycle (S,S_p)-**4** in 95% yield (entry 7). Heating (S,S_p)-**11** in MeCN at 60 °C overnight showed palladium black formation and decomposition of the starting material. In contrast, heating (S,S_p)-**4** and (S,S,S_p,S_p)-**10** separately in MeCN overnight resulted in no decomposition. Silica gel chromatography of (S,S_p)-**11** also showed signs of decomposition, as if left stationary on silica for more than 2 minutes the silica turned black.

Scheme 4. Synthesis of palladacycle (S,R_p)-5-*d*-5 via transmetalation.



With a suitable method for the synthesis of diastereomerically pure palladacycle (S,S_p)-**4** in hand we turned our attention to the synthesis of palladacycle (S,R_p)-**5** (Scheme 4). Ferrocenyloxazoline (S,R_p)-2-*d*-**1** with 90% deuterium incorporation was first synthesised as previously described by highly selective lithiation followed by a MeOH-d_4 quench.[13] Subsequent lithiation of (S,R_p)-2-*d*-**1** under poorly selective conditions[17] and quenching with mercury (II) chloride gave mercuracycle (S,R_p)-5-*d*-**13** as a single diastereoisomer in 59% yield following purification. Stirring (S,R_p)-5-*d*-**13** with two equivalents of $Pd(MeCN)_2Cl_2$ in MeCN at room temperature for 1 hour, followed by a brine wash and silica plug filtration, resulted in a successful transmetalation to give palladacycle (S,R_p)-5-*d*-**5** in 92% yield. Its ^{1}H NMR spectrum corresponded exactly with that of (S,R_p)-**5** obtained previously except for the absence of cyclopentadienyl signals at 4.51 (minor) and 4.45 (major) ppm due to deuterium incorporation (1.4 : 1 ratio of isomers).

CONCLUSION

Cyclopalladation of (*S*)-**1** has been determined to proceed with an (*S*,S_p) : (*S*,R_p) diastereomeric ratio of 3.6 : 1 using $Pd(OAc)_2$ in CH_2Cl_2 and 4 : 1 using Na_2PdCl_4 in MeOH. Palladacycles derived from (*S*)-**1** were also obtained by employing highly diastereoselective lithiation followed by addition of $PdX_2(COD)$ (X = Cl, Br) to give bispalladacycle (*S*,*S*,S_p,S_p)-**7** incorporating two ferrocenyloxazoline units. The same compound was obtained when lithium-zinc transmetalation preceded addition of $PdCl_2(MeCN)_2$. Selective mono-protodepalladation was used to generate monopalladacycles from (*S*,*S*,S_p,S_p)-**7**. Chloride-bridged monopalladacycle (*S*,S_p)-**4** was generated by transmetalation using a mercuracycle intermediate (itself generated by Li-Hg transmetalation). Key to this reaction is the use of a 2 : 1 Pd/Hg stoichiometry and a brine wash prior to product isolation. In the same way the alternative planar chiral diastereoisomer (*S*,R_p)-5-*d*-**5** was formed from the corresponding mercuracycle, itself generated selectively by use of a deuterium blocking group. The use of these palladacycles in catalysis is currently under investigation and will be published shortly.

EXPERIMENTAL SECTION

General remarks. ***Caution!*** All organomercurials are highly toxic. Extreme care is necessary when handling all products and their solutions**.** Diethyl ether and THF were distilled over sodium and benzophenone ketyl. Acetonitrile and dichloromethane were dried by distillation from calcium hydride. Methanol was dried over 4 Å molecular sieves. All cyclopalladation reactions and reactions involving the use of dry solvents were carried out under an inert atmosphere of either nitrogen or argon. Silica gel (60 Å pore size, 40 - 63 μm technical grade) and neutral aluminium oxide (Brockmann I, 50 - 200 μm) were used for chromatography.

Preparation of (*S*,S_p)-2. (*S*)-**1**[11d] (0.149 g, 0.50 mmol) and palladium acetate (0.112 g, 0.50 mmol) were added to a flame dried Schlenk tube and dissolved in dichloromethane (2.5 mL). After stirring overnight the reaction mixture was filtered through a short pad of silica to remove a black residue using dichloromethane as the eluent and the solvent removed *in vacuo*. The crude product was redissolved in a minimal amount of dichloromethane, transferred to a boiling tube, hexane layered on top and transferred to a freezer for crystals to grow. After crystal formation, the solvent was decanted off and the crystals washed with ice cold hexane to give the product as dark red crystals (0.08 g, 36 %). $[\alpha]_D^{20.2°C}$ = -1090 (*c* 0.27, $CHCl_3$). IR (film): 3089, 2963, 2930, 2870, 1609 (CN), 1577 (CO), 1507, 1411. ^{1}H NMR (500 MHz, $CDCl_3$): 4.30 - 4.26 (14H, m, Cp*H*), 4.16 (2H, apt, $^{2+3}J_{HH}$ = 7.2 Hz, C*H*H), 4.11 (2H, d, $^3J_{HH}$ = 1.6 Hz, Cp*H*), 3.78 (2H, apt, $^{2+3}J_{HH}$ = 9.2 Hz, CH*H*), 3.08 (2H, dt, $^3J_{HH}$ = 12.1, $^3J_{HH}$ = 4.1 Hz, C*H*), 2.10 - 2.04 (2H, m, C*H*), 2.03 (6H, s, CH_3), 0.93 (6H, d, $^3J_{HH}$ = 6.7 Hz, CH_3), 0.81 (6H, d, $^3J_{HH}$ = 7.0 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): 181.1 (CH_3C(O)O), 178.0 (*C*=N), 87.0 (Cp*C*), 72.2 (CH_2), 71.2 (Cp*C*), 71.0 (Cp*C*), 70.3 (Cp*C*), 66.5 (Cp*C*), 65.9 (*C*H), 63.7 (Cp*C*), 28.9 (*C*H), 23.8 (CH_3), 19.2 (CH_3'), 15.6 (CH_3). Data as previously reported.[9d]

Preparation of (*S*,S_p)-3 from (*S*,S_p)-2. (*S*,S_p)-**2** (0.083 g, 0.09 mmol) and sodium hexafluoroacetylacetonate (0.052 g, 0.22 mmol) were added to a Schlenk tube and dissolved in a 1:1 mixture of water and acetone (6 mL each). The resulting suspension was stirred vigorously overnight after which the reaction was separated between water and dichloromethane, the organic phase dried with magnesium sulphate and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, 15 % EtOAc in hexane) yielded a red solid as a single diastereoisomer (0.052 g, 99 %). R_f 0.24 (15 % EtOAc in hexane). Mp: 138 - 140 °C (under argon). $[\alpha]_D^{20.7°C}$ = -990 (*c* 0.44, $CHCl_3$). IR (film): 2963, 2930, 2873, 1630 (CN), 1604 (CO), 1510 (CO), 1477, 1261, 1208, 1148. ^{1}H NMR (500 MHz, $CDCl_3$): 6.08 (1H, s, C*H*), 4.73 (1H, dd, $^3J_{HH}$ = 2.2, $^4J_{HH}$ = 0.5 Hz, Cp*H*), 4.58 (2H, apd, $^{2+3}J_{HH}$ = 8.2 Hz, CH_2), 4.47 (1H, dd, $^3J_{HH}$ = 2.4, $^4J_{HH}$ = 0.6 Hz, Cp*H*), 4.33 (5H, s, Cp*H*), 4.31 (1H, t, $^3J_{HH}$ = 2.4 Hz, Cp*H*), 3.97 (1H, td, $^3J_{HH}$ = 8.1, $^3J_{HH}$ = 4.1 Hz, C*H*), 2.43 - 2.32 (1H, m, C*H*), 1.09 (3H, d, $^3J_{HH}$ = 6.9 Hz, CH_3), 0.96 (3H, d, $^3J_{HH}$ = 7.1 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): 180.6 (*C*=N), 174.9 (2*C*=O), 118.4 (q, $^1J_{CF}$ = 508 Hz, 2CF_3), 90.5 (*C*H), 89.9 (Cp*C*), 72.6 (CH_2), 71.4 (Cp*C*), 71.1 (Cp*C*), 70.5 (Cp*C*), 67.6 (Cp*C*), 66.2 (*C*H), 64.7 (Cp*C*), 28.6 (*C*H), 19.0 (CH_3), 15.3 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): -74.73 (CF_3), -75.71 (CF_3). High resolution MS (*m*/*z*, ASAP$^+$): $[M+H]^+$ = 609.9744, calcd for $C_{21}H_{19}F_6FeNO_3Pd+H^+$ 609.9742.

Preparation of (*S*,S_p)-4. (*S*)-**1**[11d] (0.149 g, 0.50 mmol), sodium tetrachloropalladate (0.147 g, 0.50 mmol) and sodium acetate (0.045 g, 0.55 mmol) were added to a flame dried Schlenk tube and dissolved in methanol (2 mL). After stirring overnight the solvent was removed *in vacuo* and the residue filtered through Celite™ using dichloromethane as the eluent, whereupon the solvent was removed *in vacuo* again. Purification by column chromatography (SiO_2, 100 % CH_2Cl_2) yielded an orange solid (0.065 g, 21 %). Data matches that reported below for (*S*,S_p)-**4**.

Preparation of (*S*,S_p)-4 from (*S*,S_p)-2. (*S*,S_p)-**2** (0.071 g, 0.08 mmol) and lithium chloride (0.033 g, 0.77 mmol) were added to a Schlenk tube and dissolved in a 1:1 mixture of acetone and water (5.5 mL each). After stirring overnight at room temperature the resulting suspension was filtered through a glass sinter and the orange solid washed with hexane to give the crude product. Purification by column chromatography (SiO_2, 15 % EtOAc in hexane) yielded an orange solid (0.06 g, 92 %). Data matches that reported below for (*S*,S_p)-**4**.

Preparation of (*S*,S_p)-3 from (*S*,S_p)-4. (*S*,S_p)-**4** (0.071 g, 0.081 mmol) and sodium hexafluoroacetylacetonate (0.052 g, 0.22 mmol) were added to a Schlenk tube and dissolved in a 1:1 mixture of water and acetone (6 mL each). The resulting suspension was stirred vigorously overnight after which the reaction was separated between water and dichloromethane, the organic phase dried with magnesium sulphate and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, 15 % EtOAc in Hexane) yielded a red solid as a single diastereoisomer (0.046, 99 %). Data matches that reported above for (*S*,S_p)-**3**.

Preparation of (*S*,S_p)-4 via (*S*,S_p)-2. (*S*)-**1**[11d] (0.297 g, 1.00 mmol) and palladium acetate (0.2245 g, 1.00 mmol) were added to a flame dried Schlenk tube and dissolved in dichloromethane (5 mL). After stirring overnight at room temperature, the solvent was removed *in vacuo* and the residue was redissolved in a 1:1 mixture of water and acetone (8 mL each) and lithium chloride (0.424 g, 10.00 mmol) was added. The resulting suspension was stirred vigorously overnight after which the reaction was separated between water and dichloromethane, the organic phase dried with magnesium sulphate and the solvent removed *in vacuo*. Careful purification by long column chromatography (SiO_2, 50:50 CH_2Cl_2/hexane) was able to separate the diastereoisomers yielding both as orange solids.

First to elute (*S*,R_p)-**5** (0.06 g, 14 %): R_f 0.20 (50:50 CH_2Cl_2/hexane). Mp: decomposed ~150 °C (under argon). $[\alpha]_D^{23.6°C}$ = +1215 (*c* 0.66, MeCN). IR (film): 3088, 2954, 2925, 2871, 1600 (CN), 1506. Major isomer ^{1}H NMR (500 MHz, MeCN-d^3): 4.72 - 4.65 (6H, m, CH_2 + Cp*H*), 4.45 (2H, d, $^3J_{HH}$ = 2.1 Hz, Cp*H*), 4.30 (10H, s, Cp*H*), 4.23 (2H, t, $^3J_{HH}$ = 2.3 Hz, Cp*H*), 4.02 - 3.95 (2H, m, C*H*), 2.09 - 2.01 (2H, m, C*H*), 0.91 (6H, d, $^3J_{HH}$ = 7.1 Hz, CH_3), 0.78 (6H, d, $^3J_{HH}$ = 6.9 Hz, CH_3). Minor isomer ^{1}H NMR (500 MHz, MeCN-d^3): 4.63 - 4.59 (6H, m, CH_2 + Cp*H*), 4.51 (2H, d, $^3J_{HH}$ = 2.2

Hz, Cp*H*), 4.34 (10H, s, Cp*H*), 4.31 (2H, t, $^3J_{HH}$ = 2.3 Hz, Cp*H*), 4.02 - 3.95 (2H, m, C*H*), 2.53 (2H, dq, $^3J_{HH}$ = 10.0, $^3J_{HH}$ = 7.0 Hz, C*H*), 0.83 (6H, d, $^3J_{HH}$ = 7.2 Hz, CH_3), 0.66 (6H, d, $^3J_{HH}$ = 6.9 Hz, CH_3). Major isomer ^{13}C NMR (125 MHz, MeCN-d^3): 180.3 (*C*=N), 90.2 (Cp*C*), 75.5 (Cp*C*), 73.6 (*C*H$_2$), 72.1 (Cp*C*), 71.3 (Cp*C*), 68.9 (Cp*C*), 67.5 (*C*H), 65.6 (Cp*C*), 30.8 (*C*H), 18.7 (*C*H$_3$), 14.9 (*C*H$_3$). Minor isomer ^{13}C NMR (125 MHz, MeCN-d^3): 180.5 (*C*=N), 92.0 (Cp*C*), 74.2 (Cp*C*), 73.3 (*C*H$_2$), 72.0 (Cp*C*), 71.3 (Cp*C*), 69.2 (Cp*C*), 66.9 (*C*H), 65.9 (Cp*C*), 29.7 (*C*H), 18.6 (*C*H$_3$), 14.0 (*C*H$_3$). High resolution MS (*m/z*, ASAP$^+$): [M+H]$^+$ = 876.8998, calcd for $C_{32}H_{36}Cl_2Fe_2N_2O_2Pd_2$+H$^+$ 876.9012.

Second to elute (*S*,*S*$_p$)-**4** (0.15 g, 36 %): R_f 0.17 (50:50 CH_2Cl_2/hexane). Mp: decomposed ~200 °C (under argon). $[\alpha]_D^{20.7°C}$ = -1470 (*c* 0.27, $CHCl_3$). IR (film): 3096, 2960, 2926, 2870, 1600 (CN), 1510. Major isomer ^{1}H NMR (500 MHz, MeCN-d^3): 4.67 - 4.62 (4H, m, C*H*H + Cp*H*), 4.59 - 4.51 (2H, m, CH*H*), 4.42 (2H, d, $^3J_{HH}$ = 1.8 Hz, Cp*H*), 4.27 (10H, s, Cp*H*), 4.25 (2H, t, $^3J_{HH}$ = 2.4 Hz, Cp*H*), 3.95 - 3.88 (2H, m, C*H*), 2.21 - 2.15 (2H, m, C*H*), 1.09 (6H, d, $^3J_{HH}$ = 6.9 Hz, CH_3), 0.97 (6H, d, $^3J_{HH}$ = 7.1 Hz, CH_3). Minor isomer ^{1}H NMR (500 MHz, MeCN-d^3): 4.67 - 4.62 (2H, m, Cp*H*), 4.59 - 4.51 (4H, m, CH_2), 4.47 (2H, d, $^3J_{HH}$ = 2.2 Hz, Cp*H*), 4.35 - 4.33 (2H, m, Cp*H*), 4.32 (10H, s, Cp*H*), 3.95 - 3.88 (2H, m, C*H*), 2.87 - 2.80 (2H, m, C*H*), 1.01 (6H, d, $^3J_{HH}$ = 6.9 Hz, CH_3), 0.86 (6H, d, $^3J_{HH}$ = 7.1 Hz, CH_3). Major isomer ^{13}C NMR (125 MHz, MeCN-d^3): 180.6 (*C*=N), 91.9 (Cp*C*), 74.9 (Cp*C*), 73.4 (*C*H$_2$), 72.7 (Cp*C*), 70.9 (Cp*C*), 68.6 (Cp*C*), 67.6 (*C*H), 65.0 (Cp*C*), 30.4 (*C*H), 19.2 (*C*H$_3$), 15.4 (*C*H$_3$). Minor isomer ^{13}C NMR (125 MHz, MeCN-d^3): 180.4 (*C*=N), 91.5 (Cp*C*), 73.4 (*C*H$_2$), 73.2 (Cp*C*), 72.6 (Cp*C*), 70.9 (Cp*C*), 68.9 (Cp*C*), 67.1 (*C*H), 65.2 (Cp*C*), 29.0 (*C*H), 18.9 (*C*H$_3$), 14.7 (*C*H$_3$). High resolution MS (*m/z*, ASAP$^+$): [M+H]$^+$ = 876.9014, calcd for $C_{32}H_{36}Cl_2Fe_2N_2O_2Pd_2$+H$^+$ 876.9012.

Third to elute (*S*,*S*)-**6** (0.05 g, 14 %). R_f 0.08 (50:50 CH_2Cl_2/Hexane). Mp: decomposed ~225 °C (under argon). $[\alpha]_D^{22.8°C}$ = +291 (*c* 0.35, MeCN). IR (film): 3095, 2958, 2929, 2874, 1633 (CN). ^{1}H NMR (500 MHz, MeCN-d^3): 6.27 (2H, brs, Cp*H*), 5.92 (2H, brs, Cp*H*), 5.88 (2H, brs, Cp*H*), 5.59 (2H, brs, Cp*H*), 4.69 - 4.59 (8H, m, Cp*H*), 4.43 - 4.32 (32H, m, Cp*H* + CH_2 + C*H*), 3.37 - 3.26 (2H, m, C*H*), 3.06 - 2.97 (2H, m, C*H*), 1.12 (6H, d, $^3J_{HH}$ = 6.7 Hz, CH_3), 1.08 (12H, d, $^3J_{HH}$ = 7.0 Hz, CH_3), 1.03 (6H, d, $^3J_{HH}$ = 6.7 Hz, CH_3). ^{13}C NMR (125 MHz, MeCN-d^3): 171.0 (*C*=N), 170.8 (*C*=N), 73.4 (Cp*C*), 72.8 (Cp*C*), 72.7 (4Cp*C*), 72.6 (2*C*H), 72.5 (Cp*C*), 72.1 (Cp*C*), 71.3 (2Cp*C*), 69.1 (*C*H$_2$), 68.4 (*C*H$_2$), 67.2 (Cp*C*), 67.1 (Cp*C*), 31.1 (*C*H), 30.6 (*C*H), 19.5 (*C*H$_3$), 19.0 (*C*H$_3$), 16.1 (*C*H$_3$), 15.1 (*C*H$_3$). High resolution MS (*m/z*, ASAP$^+$): [M-Cl]$^+$ = 735.0367, calcd for $C_{32}H_{38}ClFe_2N_2O_2Pd^+$ 735.0369.

Preparation of (*S*,*S*,*S*$_p$,*S*$_p$)-7. (*S*)-**1**^{11d} (0.100 g, 0.34 mmol) was added to a flame dried Schlenk tube under an inert atmosphere and dissolved in dry diethyl ether (4 mL). Tetramethylethylenediamine (0.07 mL, 0.44 mmol) was added and solution was cooled to -78 °C and stirred for 5 mins after which *s*-butyl lithium (1.4 M in hexanes) (0.31 mL, 0.44 mmol) was slowly added and stirred for 2 hours. In a separate flame dried Schlenk tube, a suspension of dibromo(1,5-cyclooctadiene)palladium(II) or dichloro(1,5-cyclooctadiene)palladium(II) (0.47 mmol) was made up in tetrahydrofuran (5 mL). Upon warming the reaction to 0 °C, the suspension was quickly added and the reaction allowed to warm to room temperature. After 30 mins, the reaction mixture was diluted with dichloromethane (5 mL) and filtered through a pad of Celite™ using dichloromethane as the eluent. The solvent was removed *in vacuo* and purification by column chromatography (SiO_2, 50/50 hexane/CH_2Cl_2) yielded an orange solid (50 % when X = Br and 42 % when X = Cl). R_f 0.41 (10 % EtOAc in hexane). Mp: decomposed ~250 °C (under argon). $[\alpha]_D^{25.5°C}$ = -2870 (*c* 0.15, $CHCl_3$). IR (film): 3099, 2954, 2918, 2871, 1608 (CN). ^{1}H NMR (500 MHz, $CDCl_3$): 4.72 (2H, d, $^3J_{HH}$ = 1.6 Hz, Cp*H*), 4.54 (2H, dd, $^2J_{HH}$ = 8.7, $^3J_{HH}$ = 5.0 Hz, C*H*H), 4.49 (2H, d, $^3J_{HH}$ = 1.8 Hz, Cp*H*), 4.46 - 4.42 (4H, m, Cp*H* + CH*H*), 4.19 (10H, s, Cp*H*), 3.89 (2H, ddd, $^3J_{HH}$ = 8.9, $^3J_{HH}$ = 4.9, $^3J_{HH}$ = 3.7 Hz, C*H*), 2.06 (2H, m, C*H*), 1.09 (6H, d, $^3J_{HH}$ = 6.8 Hz, CH_3), 0.98 (6H, d, $^3J_{HH}$ = 6.8 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): 179.1 (*C*=N), 89.3 (Cp*C*), 76.3 (Cp*C*), 75.3 (Cp*C*), 71.1 (*C*H$_2$), 70.5 (Cp*C*), 69.6 (Cp*C*), 68.6 (*C*H), 65.5 (Cp*C*), 30.6 (*C*H), 19.5 (*C*H$_3$), 15.3 (*C*H$_3$). High resolution MS (*m/z*, NSI$^+$): [M+H]$^+$ = 699.0590, calcd for $C_{32}H_{36}Fe_2N_2O_2Pd$+H$^+$ 699.0600.

Alternative preparation of (*S*,*S*,*S*$_p$,*S*$_p$)-7. (*S*)-**1**^{11d} (0.100 g, 0.34 mmol) was added to a flame dried Schlenk tube under an inert atmosphere and dissolved in dry diethyl ether (4 mL). Tetramethylethylenediamine (0.07 mL, 0.44 mmol) was added and solution was cooled to -78 °C and stirred for 5 mins after which *s*-butyl lithium (1.4 M in hexanes) (0.31 mL, 0.44 mmol) was slowly added and stirred for 2 hours. In a separate flame dried Schlenk tube, $Pd(MeCN)_2Cl_2$ (0.1309 g, 0.51 mmol) and tetrahydrofuran (15 mL) were stirred vigorously until the majority had dissolved. Whilst still at -78 °C, a solution of zinc chloride (1.9 M in 2-methyltetrahydrofuran) (0.27 mL, 0.51 mmol) was added and the reaction mixture allowed to warm to room temperature and stirred for 30 mins. Upon re-cooling to 0 °C the $Pd(MeCN)_2Cl_2$ suspension was quickly added and the reaction allowed to warm to room temperature. After 1 hour, the reaction mixture was diluted with dichloromethane (5 mL) and filtered through a pad of Celite™ using dichloromethane as the eluent. The solvent was removed *in vacuo* and purification by column chromatography (SiO_2, 10 % EtOAc in hexane) yielded an orange solid (0.046 g, 38 %). Data matches that reported above for (*S*,*S*,*S*$_p$,*S*$_p$)-**7**.

Preparation of (*S*,*S*,*S*$_p$)-8 from (*S*,*S*,*S*$_p$,*S*$_p$)-7. (*S*,*S*,*S*$_p$,*S*$_p$)-**7** (0.020 g, 0.03 mmol) was added to a flame dried Schlenk tube and dissolved in dichloromethane (1 mL). To this a solution of hydrochloric acid (2 M, in Et_2O) (14.3 µl, 0.03 mmol) was added and the solution allowed to stir for 15 mins. After complete loss of starting material the solvent was removed *in vacuo* and the resulting complex purified by column chromatography (SiO_2, 20 % EtOAc in hexane) to give a dark yellow/orange solid (0.017 g, 79 %). Mp: 106 - 108 °C. $[\alpha]_D^{24.2°C}$ = -547 (*c* 0.27, $CHCl_3$). IR (film): 3092, 2960, 2930, 2869, 1728, 1637 (CN), 1607 (CN). ^{1}H NMR (500 MHz, $CDCl_3$): 5.97 - 5.95 (1H, m, Cp*H*), 5.55 - 5.52 (1H, m, Cp*H*), 4.65 - 4.58 (2H, m, C*H* + C*H*H), 4.54 - 4.46 (3H, m, CH*H* + CH_2), 4.44 - 4.42 (2H, m, Cp*H*), 4.40 (1H, td, $^3J_{HH}$ = 2.5, $^4J_{HH}$ = 1.3 Hz, Cp*H*), 4.25 (5H, s, Cp*H*), 4.22 (5H, s, Cp*H*), 4.21 - 4.19 (2H, m, Cp*H* + C*H*), 4.01 (1H, dd, $^3J_{HH}$ = 2.2, $^4J_{HH}$ = 0.6 Hz, Cp*H*), 3.19 (1H, m, C*H*), 3.05 (1H, m, C*H*), 1.17 (3H, d, $^3J_{HH}$ = 6.7 Hz, CH_3), 1.13 (3H, d, $^3J_{HH}$ = 7.1 Hz, CH_3), 1.06 (3H, d, $^3J_{HH}$ = 6.9 Hz, CH_3), 0.92 (3H, d, $^3J_{HH}$ = 7.1 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): 179.0 (*C*=N), 170.4 (*C*=N), 90.0 (Cp*C*), 73.8 (*C*H), 72.9 (Cp*C*), 72.1 (*C*H$_2$), 72.0 (Cp*C*), 71.8 (Cp*C*), 71.6 (Cp*C*), 71.4 (Cp*C*), 71.0 (Cp*C*), 70.2 (Cp*C*), 69.9 (Cp*C*), 67.8 (*C*H$_2$), 67.7 (Cp*C*), 66.8 (Cp*C*), 66.6 (*C*H), 64.4 (Cp*C*), 30.6 (*C*H), 28.3 (*C*H), 19.7 (*C*H$_3$), 19.2 (*C*H$_3$), 15.2 (*C*H$_3$), 14.7 (*C*H$_3$). High resolution MS (*m/z*, ASAP$^+$): [M-Cl+H]$^+$ = 699.0620, calcd for $C_{32}H_{36}Fe_2N_2O_2Pd$+H$^+$ 699.0605.

Preparation of (*S*,*S*,*S*$_p$)-8 from (*S*,*S*$_p$)-4. In an NMR tube, (*S*,*S*$_p$)-**4** (0.0003 g, 0.001 mmol) and (*S*)-**1**^{11d} (0.001 g, 0.002 mmol) were dissolved in $CDCl_3$ (0.7 mL) and a ^{1}H NMR taken straight away. ^{1}H NMR data matches that reported above for (*S*,*S*$_p$,*S*$_p$)-**8**.

Preparation of (*S*,*S*$_p$)-3 from (*S*,*S*,*S*$_p$,*S*$_p$)-8. (*S*,*S*,*S*$_p$,*S*$_p$)-**8** (0.0126 g, 0.017 mmol) was dissolved in acetone (5 mL) and water (5 mL) and stirred vigorously in the presence of Na(hfacac) (0.0395 g, 0.171 mmol) at room temperature for 48 h. The reaction was separated with dichloromethane, the organics dried with magnesium sulphate and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, 15 % EtOAc in hexane) gave an orange solid (0.003 g, 25 %). Data matches that reported above for (*S*,*S*$_p$)-**3**.

Preparation of (*S*,*S*,*S*$_p$,*S*$_p$)-10. (*S*,*S*$_p$)-**9**^{13} (0.010 g, 0.019 mmol) was added to a flame dried Schlenk tube along with palladium (II) chloride (0.0034 g, 0.019 mmol). A 60/40 mixture of dichloromethane and methanol (1 mL) was added and the suspension allowed to stir at room temperature overnight. The reaction mixture was filtered through Celite™ using dichloromethane as the

eluent and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, 12 % EtOAc, 20 % CH_2Cl_2 in hexane) gave an orange solid (0.005 g, 44 %). R_f 0.40 (12 % EtOAc, 20 % CH_2Cl_2 in hexane). Mp: decomposed ~ 170 °C (under argon). $[\alpha]_D^{24.2°C}$ = -687 (*c* 0.30, $CHCl_3$). IR (film): 3094, 2958, 2930, 2872, 1628 (CN), 1603 (CN), 1509. ^{1}H NMR (500 MHz, $CDCl_3$): 5.11 (2H, dd, $^3J_{HH}$ = 2.7, $^4J_{HH}$ = 1.3 Hz, Cp*H*), 4.72 (2H, ddd, $^3J_{HH}$ = 9.8, $^3J_{HH}$ = 6.4, $^3J_{HH}$ = 3.1 Hz, C*H*), 4.69 - 4.61 (6H, m, C*H* + CH_2), 4.61 (2H, t, $^3J_{HH}$ = 2.6 Hz, Cp*H*), 4.48 (2H, dd, $^2J_{HH}$ = 8.8, $^3J_{HH}$ = 6.4 Hz, C*H*H), 4.45 (2H, dd, $^3J_{HH}$ = 2.4, $^4J_{HH}$ = 0.6 Hz, Cp*H*), 4.41 (2H, dd, $^2J_{HH}$ = 10.3, $^3J_{HH}$ = 8.8 Hz, CH*H*), 4.39 (10H, s, Cp*H*), 4.32 (2H, dd, $^3J_{HH}$ = 2.4, $^4J_{HH}$ = 1.4 Hz, Cp*H*), 4.23 (10H, s, Cp*H*), 4.19 (2H, t, $^3J_{HH}$ = 2.4 Hz, Cp*H*), 3.94 (2H, dd, $^3J_{HH}$ = 2.3, $^4J_{HH}$ = 0.7 Hz, Cp*H*), 3.32 (2H, m, C*H*), 2.82 (2H, m, C*H*), 1.23 (6H, d, $^3J_{HH}$ = 6.6 Hz, CH_3), 1.13 (6H, d, $^3J_{HH}$ = 7.1 Hz, CH_3), 1.07 (6H, d, $^3J_{HH}$ = 6.9 Hz, CH_3), 0.99 (6H, d, $^3J_{HH}$ = 6.7 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): 179.0 (*C*=N), 171.2 (*C*=N), 91.9 (Cp*C*), 87.4 (Cp*C*), 79.6 (Cp*C*), 74.9 (*C*H), 74.2 (Cp*C*), 73.3 (Cp*C*), 73.0 (CH_2), 72.9 (Cp*C*), 71.1 (Cp*C*), 70.8 (Cp*C*), 70.0 (Cp*C*), 69.7 (Cp*C*), 67.9 (Cp*C*), 67.0 (CH_2), 65.8 (*C*H), 64.7 (Cp*C*), 30.5 (*C*H), 28.6 (*C*H), 20.0 (CH_3), 19.3 (CH_3), 15.2 (CH_3), 15.1 (CH_3). High resolution MS (*m*/*z*, ASAP$^+$): [(M-$PdCl_2$)/2+H]$^+$ = 534.0202, calcd for $C_{16}H_{18}ClFeHgNO$+H$^+$534.0204.

Preparation of (*S*,*S*$_p$)-11. (*S*,*S*$_p$)-**9**[13] (0.022 g, 0.04 mmol) and bis(acetonitrile)palladium dichloride (0.021 g, 0.08 mmol) were added to a flame dried Schlenk tube and dissolved in acetonitrile (2.2 mL). The reaction was stirred for 1 h and then loaded onto a plug of silica and the product collected with 20 % EtOAc in hexane and the solvent removed *in vacuo* to give a dark red/brown solid (0.02 g, 95 %). Mp: decomposed ~100 °C (under argon). $[\alpha]_D^{23.2°C}$ = -591 (*c* 0.30, MeCN). IR (film): 3094, 2958, 2925, 2868, 1599 (CN), 1509. ^{1}H NMR (500 MHz, MeCN-d^3): 4.69 (2H, dd, $^2J_{HH}$ = 9.1, $^3J_{HH}$ = 5.8 Hz, C*H*H), 4.64 (2H, brs, Cp*H*), 4.61 (2H, apt, $^{2+3}J_{HH}$ = 9.5 Hz, CH*H*), 4.55 (2H, brs, Cp*H*), 4.41 (2H, brs, Cp*H*), 4.38 (10H, s, Cp*H*), 3.92 - 3.86 (2H, m, C*H*), 2.21 - 2.13 (2H, m, CH), 1.04 (6H, d, $^3J_{HH}$ = 6.8 Hz, CH_3)), 0.94 (6H, d, $^3J_{HH}$ = 7.0 Hz, CH_3). ^{13}C NMR (125 MHz, MeCN-d^3): 181.7 (*C*=N), 92.0 (Cp*C*), 74.2 (Cp*C*), 74.1 (CH_2), 72.0 (Cp*C*), 71.6 (Cp*C*), 69.2 (Cp*C*), 67.1 (*C*H), 66.0 (Cp*C*), 30.2 (*C*H), 19.0 (CH_3), 15.3 (CH_3). High resolution MS (*m*/*z*, ASAP$^+$): [M-$HgCl_2$+H]$^+$ = 876.9036, calcd for $C_{32}H_{36}Cl_2Fe_2N_2O_2Pd_2$+H$^+$ 876.9012.

Preparation of (*S*,*S*$_p$)-12. (*S*,*S*$_p$)-**4** (0.025 g, 0.029 mmol) and triphenylphosphine (0.015 g, 0.057 mmol) were added to a flame dried Schlenk tube and dissolved in dichloromethane (1 mL) and stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and purification by column chromatography (SiO_2, 20 % EtOAc in hexane) yielded a deep orange solid (0.038 g, 99 %). R_f 0.21 (20 % EtOAc in hexane). Mp: decomposed ~230 °C (under argon). $[\alpha]_D^{22.8°C}$ = -825 (*c* 0.26, MeCN). IR (film): 3077, 3052, 2958, 2925, 2867, 1618 (CN), 1503. ^{1}H NMR (500 MHz, MeCN-d^3): 7.78 - 7.72, (6H, m, Ph*H*), 7.53 - 7.49 (3H, m, Ph*H*), 7.48 - 7.43 (6H, m, Ph*H*), 4.67 - 4.57 (2H, m, CH_2), 4.47 (1H, d, $^3J_{HH}$ = 1.9 Hz, Cp*H*), 4.18 (1H, ddd, $^3J_{HH}$ = 10.2, $^3J_{HH}$ = 6.3, $^3J_{HH}$ = 4.2 Hz, C*H*), 4.02 (1H, apt, $^{3+3}J_{HH}$ = 2.1 Hz, Cp*H*), 3.97 (5H, s, Cp*H*), 3.04 (1H, brs, Cp*H*), 2.87 (1H, brs, C*H*), 1.06 (3H, d, $^3J_{HH}$ = 6.9 Hz, CH_3), 0.92 (3H, d, $^3J_{HH}$ = 7.2 Hz, CH_3). ^{13}C NMR (125 MHz, MeCN-d^3): 179.9 (*C*=N), 135.6 (d, $^2J_{CP}$ = 11.7 Hz, Ph*C*), 132.9 (d, $^1J_{CP}$ = 51.3 Hz, Ph*C*), 131.6 (Ph*C*), 129.1 (d, $^3J_{CP}$ = 10.8 Hz, Ph*C*), 94.6 (Cp*C*), 75.9 (d, $^3J_{CP}$ = 8.7 Hz, Cp*C*), 74.2 (Cp*C*), 73.3 (CH_2), 70.9 (Cp*C*), 69.4 (Cp*C*), 68.0 (d, $^3J_{CP}$ = 3.1 Hz, *C*H), 65.6 (Cp*C*), 29.4 (*C*H), 19.2 (CH_3), 15.5 (CH_3). ^{31}P NMR (202 MHz, MeCN-d^3): 37.49 (*P*Ph_3). High resolution MS (*m*/*z*, ASAP$^+$): [M-Cl]$^+$ = 664.0711, calcd for $C_{34}H_{33}FeNOPPd^+$ 664.0699.

Preparation of (*S*,*S*$_p$)-4 from (*S*,*S*$_p$)-9. (*S*,*S*$_p$)-**9**[13] (0.020 g, 0.04 mmol) and bis(acetonitrile)palladium dichloride (0.020 g, 0.08 mmol) were added to a flame dried Schlenk tube and dissolved in acetonitrile (2 mL). The reaction was stirred for 1 h and then diluted with dichloromethane (20 mL) and washed with brine twice. All of the organic layer was loaded onto a plug of silica and the product collected with 30 % EtOAc in hexane and the solvent removed *in vacuo* to give a deep red solid (0.016 g, 95 %). Data matches that reported above for (*S*,*S*$_p$)-**4**.

Preparation of (*S*,*R*$_p$)-5-*d*-5. (*S*,*R*$_p$)-5-*d*-**13**[13] (0.020 g, 0.04 mmol) and bis(acetonitrile)palladium dichloride (0.020 g, 0.08 mmol) were added to a flame dried Schlenk tube and dissolved in acetonitrile (2 mL). The reaction was stirred for 1 h and then diluted with dichloromethane (20 mL) and washed with brine twice. All of the organic layer was loaded onto a plug of silica and the product collected with 30 % EtOAc in hexane and the solvent removed *in vacuo* to give a deep red solid (0.015 g, 92 %). NMR data matches that reported above for (*S*,*R*$_p$)-**5** except for the absence of a cyclopentadienyl signals at 4.51 (minor) and 4.45 (major) ppm due to deuterium incorporation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Copies of the ^{1}H, ^{13}C, ^{31}P NMR and X-ray crystallography details (PDF file). CCDC 1938231, 1938232, 1938233 and 1938234 contain supplementary X-ray crystallographic data for (*S*,*S*$_p$)-**3,** (*S*,*S*$_p$)-**4,** (*S*,*S*)-**6** and (*S*,*S*,*S*$_p$,*S*$_p$)-**10**, respectively. This data can be obtained free of charge via http://www.ccdc. cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, Union Road, Cambridge, CB2 1EZ; fax(+44) 1223-336-033 or e-mail: deposit@ccdc.cam.ac. uk. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Dupont, J.; Consorti, C. S.; Spencer, J. *The Potential of Palladacycles: More Than Just Precatalysts*. *Chem. Rev*. **2005**, *105*, 2527-2571. (b) Palladacycles: Synthesis, Characterization and Applications. Ed. Dupont, J. Pfeffer, M. Wiley-VCH, Weinheim, 2008.

(2) Yam, V. W.-W.; Au, V. K.-M.; Leung, S. Y.-L. Light-Emiting Self-Assembled Materials Based on d^8 and d^{10} Transition Metal Complexes. *Chem. Rev*. **2015**, *115*, 7589-7728.

(3) (a) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riermeier, T. H.; Öfele, K.; Beller, M. Palladacycles: Efficient New Catalysts for the Heck Vinylation of Aryl Halides. *Chem. Eur. J.* **1997**, *3*, 1357-1364. (b) Kinzel, T.; Zhang, Y.; Buchwald, S. L. A New Palladium Precatalyst Allows for the Fast Suzuki-Miyaura Coupling Reactions of Unstable Polyfluorophenyl and 2-Heteroaryl Boronic Acids. *J. Am. Chem. Soc.* **2010**, *132*, 14073-14075. (c) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. Design and Preparation of New Palladium Precatalysts for C-C and C-N Cross-Coupling Reactions. *Chem. Sci.* **2013**, *4*, 916-920.

(4) (a) Nomura, H.; Richards, C. J. Allylic Imidate Rearrangements Catalyzed by Planar Chiral Palladacycles. *Chem. Asian J.* **2010**, *5*, 1726-1740. (b) Dunina, V. V.; Gorunova, O. N.; Zykov, P. A.; Kochetkov, K. A. Cyclopalladated Complexes in Enantioselective

Catalysis. *Russ. Chem. Rev*. **2011**, *80*, 51-74. (c) Mo, D.-L.; Zhang, T.-K.; Ge, G.-C.; Huang, X.-J.; Ding, C.-H.; Dai, L.-X.; Hou, X.-L. The Applications of Palladacycles as Transition-Metal Catalysts in Organic Synthesis. *Synlett* **2014**, *25*, 2686-2702. (d) Cannon, J. S.; Overman, L. E. Palladium(II)-Catalyzed Enantioselective Reactions Using COP Catalysts. *Acc. Chem. Res*. **2016**, *49*, 2220-2231.

(5) (a) Dyker, G. Palladacycles as Reactive Intermediates. *Chem. Ber/Recueil* **1997**, *130*, 1567-1578. (b) Dastbaravardeh, N.; Christakakou, M.; Haider, M.; Schnürch, M. Recent Advances in Palladium-Catalyzed C(sp^3)-H Activation for the Formation of Carbon-Carbon and Carbon-Heteroatom Bonds. *Synthesis* **2014**, *46*, 1421-1439.

(6) Timsina, Y. N.; Gupton, B. F. ; Ellis, K. C. Palladium-Catalyzed C-H Amination of C(sp^2) and C(sp^3)-H Bonds: Mechanism and Scope for N-Based Molecule Synthesis. *ACS Catal.* **2018**, *8*, 5732-5776.

(7) Trofimenko, S. Some Studies of the Cyclopalladation Reaction. *Inorg. Chem.* **1973**, *12*, 1215-1221.

(8) (a) Sokolov, V. I.; Troitskaya, L. L.; Reutov, O. A. Asymmetric Cyclopalladation of Dimethylaminomethylferrocene. *J. Organomet. Chem.* **1979**, *182*, 537-546. (b) Günay, M. E.; Richards, C. J. Synthesis of Planar Chiral Phosphapalladacycles by *N*-Acyl Amino Acid Mediated Enantioselective Palladation. *Organometallics* **2009**, *28*, 5833-5836. (c) Cassar, D. J.; Ilyashenko, G.; Ismail, M.; Woods, J.; Hughes, D. L.; Richards, C. J. Enantioselective Synthesis and Application to the Allylic Imidate Rearrangement of Amine-Coordinated Palladacycle Catalysts of Cobalt Sandwich Complexes. *Chem. Eur. J.* **2013**, *19*, 17951-17962.

(9) (a) Hollis, T. K.; Overman, L. E. Cyclopalladated Ferrocenyl Amines as Enantioselective Catalysts for the Rearrangement of Allylic Imidates to Allylic Amides. *Tetrahedron Lett.* **1997**, *38*, 8837-8840. (b) Stevens, A. M.; Richards, C. J. Synthesis and Highly Diastereoselective Palladation of (η^5-(*S*)-2-(4-Methylethyl)oxazolinylcyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt. *Organometallics* **1999**, *18*, 1346-1348. (c) Weiss, M. E.; Fischer, D. F.; Xin, Z.-Q.; Jautze, S.; Schweizer, W. B.; Peters, R. Practical, Highly Active, and Enantioselective Ferrocenyl-Imidazoline Palladacycle Catalysts (FIPs) for the Aza-Claisen Rearrangement of *N*-*para*-Methoxyphenyl Trifluoroacetimidates. *Angew. Chem. Int. Ed*. **2006**, *45*, 5694-5698. (d) Xia, J.-B.; You, S.-L. Carbon-Carbon Bond Formation through Double sp^2 C-H Activations: Synthesis of Ferrocenyl Oxazoline Derivatives. *Organometallics* **2007**, *26*, 4869-4871. (e) Fischer, D.F.; Barakat, A.; Xin, Z.-q.; Weiss, M. E.; Peters, R. The Asymmetric Aza-Claisen Rearrangement: Development of Widely Applicable Pentaphenylferrocenyl Palladacycle Catalysts. *Chem. Eur. J*. **2009**, *15*, 8722-8741. (f) Cassar, D. J.; Roghzai, H.; Villemin, D.; Horton, P. N.; Coles, S. J.; Richards, C. J. Chirality Control in Planar Chiral Cobalt Oxazoline Palladacycles. *Organometallics* **2015**, *34*, 2953-2961.

(10) (a) Otsuka, S.; Nakamura, A.; Kano, T.; Tani, K. Partial Resolution of Racemic Tetriary Phosphines with an Asymmetric Palladium Complex. *J. Am. Chem. Soc.* **1971**, *93*, 4301-4303. (b) Moyano, A.; Rosol, M.; Moreno, R. M.; López, C.; Maestro, M. A. Oxazoline-Mediated Interannular Cyclopalladation of Ferrocene: Chiral Palladium(II) Catalysts for the Enantioselective Aza-Claisen Rearrangement. *Angew. Chem. Int. Ed*. **2005**, *44*, 1865-1869.

(11) (a) Sammakia, T.; Latham, H. A. Ligand Effects on the Stereochemistry of the Metalation of Chiral Ferrocenyloxazolines. *J. Org. Chem*. **1995**, *60*, 6002-6003. (b) Richards, C. J.; Damalidis, T.; Hibbs, D. E.; Hursthouse, M. B. Synthesis of 2-[2-(Diphenylphosphino)ferrocenyl]oxazoline Ligands. *Synlett* **1995**, 74-76. (c) Nishibayashi, Y.; Uemura, S. Asymmetric Synthesis and Highly Diastereoselective *ortho*-Lithiation of Oxazolinylferrocenes. *Synlett* **1995**, 79-81. (d) Richards, C. J.; Mulvaney, A. W. Synthesis of Phosphinoferrocenyloxazolines. New Ligands for Asymmetric Catalysis. *Tetrahedron: Asymmetry* **1996**, *7*, 1419-1430.

(12) (a) Donde, Y.; Overman, L. E. High Enantioselection in the Rearrangement of Allylic Imidates with Ferrocenyl Oxazoline Catalysts. *J. Am. Chem. Soc.* **1999**. *121*, 2933-2934. (b) Anderson, C. E.; Donde, Y.; Douglas, C. J.; Overman, L. E. Catalytic Asymmetric Synthesis of Chiral Allylic amines. Evaluation of Ferrocenyloxazoline Palladacycle Catalysts and Imidate Motifs. *J. Org. Chem*. **2005**, *70*, 648-657.

(13) The synthesis of (S,S_p)-2-(2'-(4'-isopropyl)oxazolinyl)-1-bromoferrocene followed by oxidative addition with a Pd(0) source was also explored as an alternative route. See supporting information. Related chemistry with iodoferrocene derivatives is known. See reference 12.

(14) (a) Chval, Z.; Sip, M.; Burda, J. V. The Trans Effect in Square-Planar Platinum(II) Complexes – A Density Functional Study. *J. Comp. Chem.* **2008**, *29*, 2370-2381. (b) Tsipis, A. C. *Trans*-Philicity (*trans*-Influence/*trans*-Effect) Ladders for Square Planar Platinum(II) Complexes Constructed by ^{35}Cl NMR Probe. *J. Comp. Chem.* **2019**, 40, 2550-2562.

(15) Arthurs, R. A.; Hughes, D. L.; Horton, P. N.; Coles, S. J.; Richards, C. J. Application of Transmetalation to the Synthesis of Planar Chiral and Chiral-at-Metal Iridacycles. *Organometallics* **2019**, *38*, 1099-1107.

(16) Related complexes containing a mercury double halide bridge are known. See: (a) Brookes, P. R.; Shaw, B. L. Mercuric Halide Adducts of Tertiary Phosphine or Tertiary Arsine Complexes of Palladium(II) and Platinum(II). *J. Chem. Soc., Dalton Trans.* **1973**, 783-788. (b) Nesmeyanov, A. N.; Rubezhov, A. Z. Allylmercury Compounds, Convenient Reagents for Synthesis of π-Allyl Derivatives of Transition Metals. *J. Organomet. Chem.* **1979**, *164*, 259-275.

(17) Arthurs, R. A.; Richards, C. J. Deuterium as a Stereochemically Invisible Blocking Group for Chiral Ligand Synthesis. *Org. Lett*. **2017**, *19*, 702-705.

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