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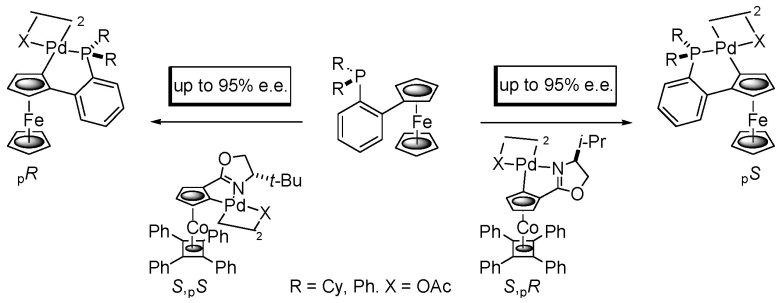

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Synthesis of Planar Chiral Phosphapalladacycles by Highly Enantioselective Transcyclopalladation

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Two areas of organometallic chemistry that have recently attracted widespread interest are the application of planar chiral ferrocenes to asymmetric catalysis[1] and the use of palladacycles as catalysts and precatalysts in organic synthesis.[2] Related studies with nonracemic planar chiral palladacycles, first synthesized by the pioneering work of Sokolov,[3] have been hampered by the absence of methodology for the stereoselective introduction of palladium. We recently reported two solutions to this problem with the highly diastereoselective palladation of **1** and **2** using $Pd(OAc)_2$ to give diastereomeric palladacycles (S,$_pR$)-**3a**[4] and (S,$_pS$)-**4a**[5] (Scheme 1). Further work has revealed **3b** to be an excellent catalyst for the enantioselective aza-Claisen rearrangement of allylic imidates.[6]

Palladacycles may also be synthesized by exchange of cyclometalated ligands,[7] typically the transfer of palladium from a C,N- to a C,P-chelate driven by the greater phosphorus−palladium bond strength of the latter. The term transcyclometalation was coined to define a subcategory of this process where the reaction proceeds without the formation of dissociated metal salts.[8] Asymmetric transcyclopalladation was recently reported,[9] the reaction between *tert*-butyldi(*o*-tolyl)phosphine and cyclopalladated (*R*)-α-*tert*-butylbenzylamine in toluene[10] resulting in a phosphapalladacycle with the enantiomeric excess quoted as varying between 72 and 91%. However, extension of this procedure to the synthesis of a planar chiral complex derived from di-*tert*-butylferrocenylmethylphosphine was hampered by the absence of both reactivity and selectivity (26% yield, 44% ee). In a recent study, we reported the ease with which phosphine **5** reacts with $Pd(OAc)_2$ to give racemic **7a** after 1 h at room temperature.[11] In view of the lability of this ferrocene substrate toward palladation, and the high enantioselectivity exhibited by cobalt oxazoline palladacycle **3b** in catalysis, we chose to explore the reaction between these different metallocenes as a means of achieving the first highly enantioselective synthesis of planar chiral phosphapalladacycles.

Phosphine **5** (^{31}P δ = −11.81) was heated at 80 °C with palladacycle **3a** in d^8-toluene and the reaction monitored by ^{31}P NMR. Following complete conversion to **7a** (^{31}P δ = 45.05), separation of the released oxazoline **1** by column chromatography on SiO_2 resulted in isolation of the phosphapalladacycle as its corresponding chloride-bridged dimer **7b**,[12] acetate/chloride ligand exchange occurring with residual chloride (ca. 0.002%) present in the silica employed for chromatography. The enantiomeric excess of the resultant complex was determined as 91% by ^1H and ^{31}P NMR following addition of (*S*)-α-methylbenzylamine (Table 1, entry 1).[13] Application of the chloride-bridged palladacycle **3b** gave a poor conversion to **7b** after 24 h (entry 2). Use of **3a** at 70 °C resulted in an increase in the enantioselectivity (entry 3), though further reductions in temperature made little difference in terms of the selectivity but significantly prolonged the reaction time (entries 4 and 5). Application of diastereomeric palladacycle **4a**, which has the opposite configuration of planar chirality, led to a complete reversal in the enantioselectivity of transcyclopalladation (entry 6).

Table 1. Investigative Synthesis of **7b** by Transcyclopalladation[a]

entry	reagent	temp	time	ee (configuration)
1	**3a**	80 °C	6 h[b]	91% ($_pS$)
2	**3b**	80 °C	24 h[c]	n/d
3	**3a**	70 °C	10 h[b]	95% ($_pS$)
4	**3a**	60 °C	20 h[b]	95% ($_pS$)
5	**3a**	50 °C	48 h[b]	94% ($_pS$)
6	**4a**	70 °C	3 h[b]	95% ($_pR$)

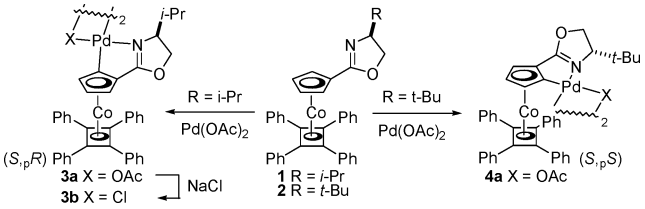
[a] Reactions carried out with 33 μmol of **5** with 17 μmol of cobalt palladacycle dimers in d^8-toluene (0.75 mL). [b] Conversion determined to be >95% by ^{31}P NMR. [c] Reaction incomplete after 24 h (ca. 15% conversion), the major product having a broad peak (^{31}P δ) at approximately 50 ppm.

Table 2. Preparative Synthesis of **7b**/**8b** by Transcyclopalladation[a]

entry	substrate	reagent	product (yield)	ee[13,14] (configuration)	recovered oxazoline
1	**5**	**3a**	**7b** (99%)	95% ($_pS$)	**1** (81%)
2	**5**	**4a**	**7b** (93%)	95% ($_pR$)	**2** (98%)
3	**6**	**3a**	**8b** (97%)	78% ($_pS$)	**1** (88%)
4	**6**	**4a**	**8b** (89%)	92% ($_pR$)	**2** (88%)

[a] Reactions typically carried out with 1.0 mmol of **5** or **6** with 0.51 mmol of cobalt palladacycle dimer in toluene (15 mL) at 70 °C for 5 h.

Scheme 1



The synthesis of the two enantiomers of **7b** was repeated on a preparative scale, and the methodology extended to the generation of the diphenylphosphine-based palladacycles ($_pS$)- and ($_pR$)-**8b**, albeit with slightly lower enantioselectivities (Table 2).[14] At the end of each reaction, acetate/chloride ligand exchange permitted separation by column chromatography of the product palladacycle and the starting cobalt oxazolines **1** or **2**.[15]

The absolute configuration of palladacycle **7b**, arising from reaction with **3a** (Table 2, entry 1), was determined as $_pS$ by an X-ray crystal structure analysis (Figure 1),[16] and the absolute configurations of the enantiomers of **8b** were determined by comparison of specific rotations.[17]

Further analysis of the reaction between **5** and **3a** by ^{31}P NMR revealed the presence a single additional broad signal at ca. 56 ppm that disappeared on completion of the reaction. The identity of this intermediate as a monomeric adduct from these two reactants was confirmed by mass spectrometry.[18] Similarly, the major product

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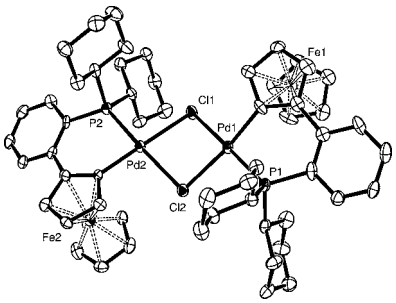
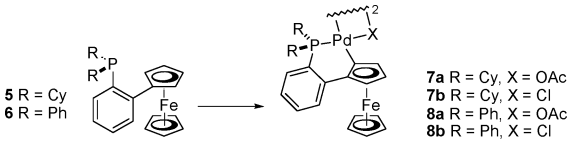
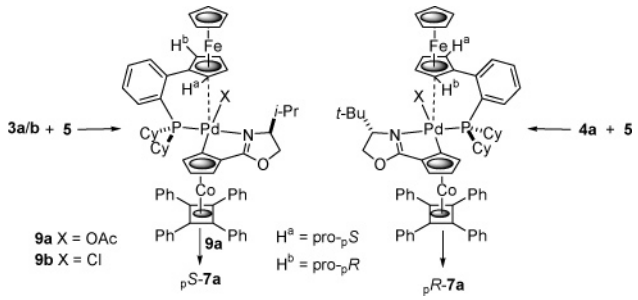


Figure 1. Representation of the crystal structure of ($_p$*S*)-**7b**.

Scheme 2



Scheme 3



from the reaction of **5** and **3b** (Table 1, entry 2) was isolated and also shown to be a simple combination of these two reactants. It has previously been established that addition of triphenylphosphine to related aryloxazoline palladacycles containing halogen bridging ligands gave adducts with the phosphine ligated trans to the oxazoline nitrogen.[19] All of this evidence points toward the observed intermediates in the reaction of palladacycles **3a** and **3b** with phosphine **5** having structures **9a** and **9b**, respectively. In view of the greater reactivity of chloride compared to oxygen-based nucleophiles in the substitution reactions of related platinum(II) complexes,[20] the reciprocal ease of acetate ligand loss may account for the success of transcyclopalladation with **3a** compared to **3b**. Palladation of benzene derivatives has been shown to proceed via the intermediacy of a cationic Pd(II)-arenium species.[21] Formation of a ferrocene equivalent by approach of this group from the side opposite the bulky tetraphenylcyclobutadiene group accounts for the observed ($_p$*S*)-product configuration (Scheme 3).[22] As palladacycle **4a** gave the opposite ($_p$*R*)-phosphapalladacycle, the origin of stereoselection in this instance may be explained by a pseudo-enantiomeric reaction pathway. These models rationalize how the planar chirality of metallocenes **3a** and **4a** control the stereoselectivity of palladium transfer, the *i*-Pr or *t*-Bu oxazoline substituents playing little part in the enantiodiscrimination.

In conclusion, both enantiomers of planar chiral phosphapalladacycles **7b** and **8b** are available in high enantioselectivity by utilizing oxazolines **1** and **2**, respectively, as recoverable palladium transfer reagents. In our ongoing investigations, we are exploring the potential of these scalemic phosphapalladacycles as catalysts for a variety of synthetic protocols.

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Supporting Information Available: Experimental procedures and characterization of **5**, **6**, **7b**, **8b**, and **9b**, together with details of the X-ray crystal structure determination of **7b** (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Cyclopalladated ligand exchange reactions have previously been performed either in or with acetic acid, resulting in a dissociative mechanism via protonolysis of the Pd−C bond. Use of these conditions with 8-ethylquinoline and scalemic cyclopalladated α-methylbenzylamine gave no asymmetric induction in the resulting exchange reaction; see ref 7b.

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(12) ^{31}P NMR (δ, d^8-toluene): 38.85, 39.75 (3:2 ratio). Racemic **7b** gave: 38.98, 39.71, 39.92 (3:2:1.5 ratio).

(13) **7b** + ca. 10 equiv of (*S*)-α-methylbenzylamine ($CDCl_3$). ^{1}H NMR: ($_p$*S*)-**7b** 3.94, ($_p$*R*)-**7b** 3.97 (5H, s, C_5H_5). ^{31}P NMR: ($_p$*S*)-**7b** 36.81, ($_p$*R*)-**7b** 36.90.

(14) **8b** + ca. 10 equiv of (*R*)-1-(1-naphthyl)ethylamine. ^{1}H NMR: ($_p$*S*)-**7b** 3.92, ($_p$*R*)-**7b** 3.86 (5H, s, C_5H_5).

(15) Representative procedure: A solution of **5** (0.460 g, 1.00 mmol) and **3a** (0.794 g, 0.53 mmol) in toluene (20 mL) was heated for 5 h at 70 °C. After cooling, the reaction mixture was shaken for 10 min with a saturated aqueous solution of sodium chloride (20 mL); the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organics were dried ($MgSO_4$); the solvent was removed in vacuo and the residue column chromatographed (SiO_2, 1% NEt_3, CH_2Cl_2) to give first **1** (0.508, 86%) followed by **7b** as an orange/red foam (0.598 g, 99%).

(16) Crystal data for ($_p$*S*)-**7b** (crystallized from $CHCl_3$). $C_{58}H_{70}Cl_8Fe_2P_2Pd_2$, M = 1437.18, monoclinic, a = 13.5209(6), b = 15.1921(7), c = 15.0232(6) Å, α = 90.00, β = 108.483(3), γ = 90.00°, V =2926.7(2) Å^3, space group $P2_1$, Z = 2, D_c = 1.631 Mg/m^3, μ = 1.548 mm^{-1}, reflections measured 36 676, unique reflections 13 167 with R_{int} = 0.0776, T = 120(2) K. Final R indices {$I > 2\sigma(I)$] R_1 = 0.0594, wR_2 = 0.1068 and for all data R_1 = 0.0855, wR_2 = 0.1150. Absolute structure parameter 0.03(2).

(17) Rotational data: ($_p$*S*)-**7b** (95% ee) $[\alpha]_D^{25}$ −551 (*c* 0.1, CH_2Cl_2), ($_p$*S*)-**8b** (78% ee) $[\alpha]_D^{25}$ −480 (*c* 0.1, CH_2Cl_2).

(18) *m*/*z* (FAB) 1149−1161 (**9a**-OAc). Confirmed by comparison of actual and theoretical isotope patterns (see Supporting Information).

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(22) Further studies on the detailed mechanism are beyond the scope of this communication. We only note the possibility of consecutive 1,2-sigmatropic hydrogen shifts via a palladium(IV) intermediate as a mechanism for hydrogen transfer between the iron and cobalt metallocenes. For a detailed investigation into the intermediates observed in a related transcycloplatination with a PCP pincer ligand, see ref 8a.

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