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Synthesis of Planar Chiral Phosphapalladacycles by *N*-Acyl Amino Acid Mediated Enantioselective Palladation

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Summary: Reaction of 2-(dicyclohexylphosphino)phenylferrocene with sodium tetrachloropalladate in the presence of 1 equiv of (R)-N-acetylphenylalanine in MeOH/H_2O/CH_2Cl_2 at pH 8 resulted in the formation of bis(μ-chloro)bis[2-(2-(dicyclohexylphosphino)phenyl)ferrocene-C^1,P]dipalladium(II) with a 59% enantiomeric excess of the $_pS$ planar chiral palladacycle. Similarly, (dimethylaminomethyl)ferrocene gave ($_pS$)-bis(μ-chloro)bis[2-(dimethylaminomethyl)ferrocene-C^1,P]-dipalladium(II) in 96% ee. An intramolecular isotope effect of 2.3 was observed for the palladation of 2-(diphenylphosphino)-phenylferrocene under these conditions.

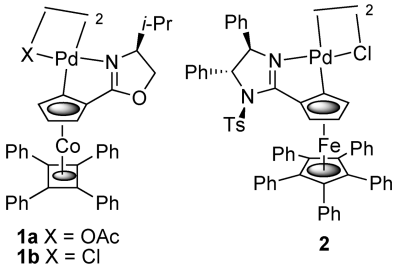
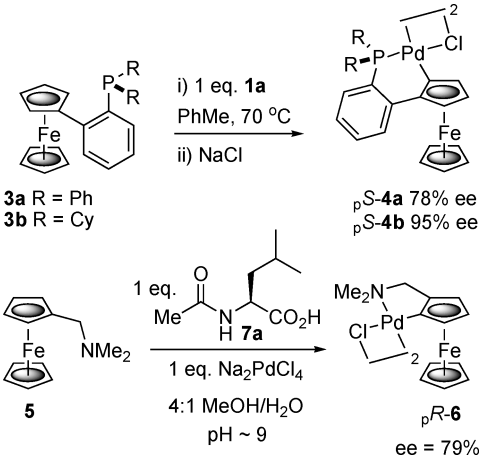


Figure 1. Metallocene-based planar chiral palladacycles.

Metallocene-based planar chiral palladacycles are of increasing importance in asymmetric organic synthesis, principally due to the application of complexes **1** and **2** (Figure 1) and similar systems as highly enantioselective catalysts for the allylic imidate rearrangement[1] and related reactions.[2] The majority of scalemic planar chiral palladacycles are obtained by resolution or by the use of a chiral auxiliary to control diastereoselective palladadation,[3] the synthesis of **1** and **2** falling into this latter category.[1e,4] In contrast, examples of enantioselective palladation are rare. One of us recently reported the application of **1a** as a reagent for the transcyclopalladation of prochiral ferrocenes **3**, resulting in the highly enantioselective generation of phosphapalladacycles **4** (Scheme 1).[5,6] In 1979 Sokolov and others described

Scheme 1. Known Methods for the Generation of Planar Chiral Metallocenes by Enantioselective Palladation



the reaction of (dimethylaminomethyl)ferrocene (**5**) with sodium tetrachloropalladate together with 1 equiv of (*S*)-*N*-acetylleucine (**7a**), which resulted in the isolation of palladacycle **6** in up to 79% ee (Scheme 1).[7] There is currently a great deal of interest in transition-metal C−H activation chemistry and its application to arene substitution,[8] including enantioselective functionalization.[9] In light of this and the potential application of phosphapalladacycles **4** in organic synthesis, we chose to apply the Sokolov protocol to prochiral substrates **3**. The results of this investigation are reported in this note.

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Results and Discussion

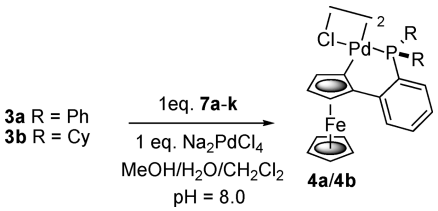
Using an adaptation of the Sokolov methodology,[7] a $MeOH/CH_2Cl_2$ solution of phosphine **3a** was added to an aqueous solution of 1:1 (*S*)-*N*-acetylleucine (**7a**)/sodium hydroxide with the pH adjusted to 8.0 using additional sodium hydroxide. After the mixture was stirred overnight at room temperature, the product ($_pR$)-**4a** was isolated from the reaction mixture in 88% yield and 36% ee (Scheme 2 and Table 1, entry 1). The ee and absolute configuration were determined as previously described.[5] Lowering and increasing the pH of the reaction mixture to 7.0 and 9.0, respectively, resulted in a slight decrease in both yield and enantioselectivity (entries 2 and 3). A number of other *N*-acetyl amino acid derivatives were screened at pH 8.0 (entries 4−7), and although most proved inferior to *N*-acetylleucine, *N*-acetylphenylalanine gave a slightly improved ee of 42%. Replacement of the acetyl group with a *p*-toluenesulfonyl group (entries 8 and 9), Boc group (entry 10), benzoyl group (entry 11), and trifluoroacetyl group (entry 12) all resulted in a lower ee. The carbonyl or sulfonyl nitrogen substituents are required to solubilize the amino acid under the conditions used, as revealed by the use of (*S*)-phenylalanine (entry 13). The amino acid was found to be largely insoluble, and ($_pR$)-**4a** was isolated with an ee of 26% and a significantly reduced yield (also 26%). Of the nitrogen substituents screened, the acetyl group is clearly the optimum group; more electron-withdrawing and/or larger substituents proved inferior.

Repetition of these reactions on dicyclohexylphenylphosphine **3b** (entries 14−23) resulted in similar trends, albeit with generally higher enantioselectivities. Again *N*-acetylphenylalanine proved to be the most selective, resulting in an ee of 59% (entry 16). These results reveal that amino acid derivatives containing "long" α-substituents such as isobutyl, and notably benzyl, gave the highest enantioselectivities in contrast to the isopropyl substituent of *N*-acetylvaline, which was conspicuously unsuccessful.

The original Sokolov substrate, (dimethylaminomethyl)ferrocene (**5**), was reinvestigated using the most enantioselective conditions identified for phosphines **3a**,**b**, in order to see if the previously reported enantiomeric excess of 79% could be improved. As the ee of the product palladacycle **6** had previously been determined using polarimetry,[7] we sought a more accurate alternative by reacting *rac*-**6** with (*S*)-proline, which gave (S,$_pS$)-**8** and its S,$_pR$ diastereoisomer with well-separated methyl and cyclopentadienyl singlets in the resulting ^{1}H NMR spectrum. Using this technique with the product of (*R*)-*N*-acetylphenylalanine-mediated palladation, obtained in a yield of 88%, resulted in the determination of an ee of 96% (Scheme 3). The absolute configuration of the product ($_pS$)-**6** was determined by polarimetry.[7] Under otherwise identical conditions (*S*)-*N*-acetylleucine gave a 74% yield of ($_pR$)-**6** with an ee of 95%.

We also investigated the effect of changing the number of equivalents of the amino acid derivative on the yield and enantioselectivity of palladation (Table 2). Starting with phosphine **3b**, doubling the amount of *N*-acetylphenylalanine to 200 mol % with respect to the substrate and sodium tetrachloropalladate resulted in a 81% yield and a small increase in the ee to 65% (entry 1). Decreasing the amount to just 10 mol % with **3b** resulted in both a low yield and low ee (entry 2), whereas amine **5** with 10 mol % (*R*)-*N*-acetylphenylalanine also gave a poor yield but with little erosion of enantioselectivity compared to the stoichiometric reaction

Scheme 2. N-protected Amino Acid Mediated Enantioselective Palladation of 3a,b



Scheme 3. Enantioselective Palladation of (dimethylaminomethyl)ferrocene (5)

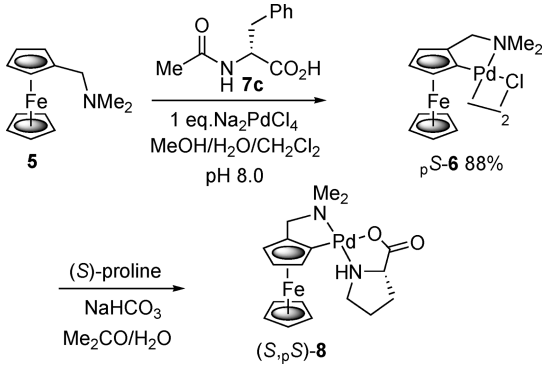


Table 1. N-protected Amino Acid Mediated Enantioselective Palladation of 3a,b[a]

		product **4a**			product **4b**	
entry[a]	ligand	yield, %	ee, % (config)	entry	yield, %	ee, % (config)
1	(*S*)-*N*-acetylleucine (**7a**)	88	36 ($_pR$)	14	77	31 ($_pR$)
2[b]	(*S*)-*N*-acetylleucine (**7a**)	70	29 ($_pR$)			
3[c]	(*S*)-*N*-acetylleucine (**7a**)	84	31 ($_pR$)			
4	(*S*)-*N*-acetylvaline (**7b**)	69	∼0	15	72	∼0
5	(*R*)-*N*-acetylphenylalanine (**7c**)	**80**	**42 ($_pS$)**	16	**85**	**59 ($_pS$)**
6	(*S*)-*N*-acetyltryptophan (**7d**)	71	11 ($_pR$)	17	65	12 ($_pR$)
7	(*S*)-*N*-acetylproline (**7e**)	77	13 ($_pS$)	18	69	8 ($_pS$)
8	(*S*)-*N*-(*p*-toluenesulfonyl)leucine (**7f**)	85	18 ($_pR$)	19	81	46 ($_pR$)
9	(*S*)-*N*-(*p*-toluenesulfonyl)phenylalanine (**7g**)	72	13 ($_pR$)	20	73	32 ($_pR$)
10	(*S*)-*N*-Boc-leucine (**7h**)	78	9 ($_pR$)	21	82	8 ($_pR$)
11	(*S*)-*N*-benzoylphenylalanine (**7i**)	69	12 ($_pS$)	22	85	10 ($_pS$)
12	(*S*)-*N*-(trifluoroacetyl)phenylalanine (**7j**)	50	5 ($_pR$)	23	60	8 ($_pS$)
13	(*S*)-phenylalanine (**7k**)	26	26% ($_pR$)			

[a] All reactions at pH 8.0 unless otherwise stated. [b] pH 7.0. [c] pH 9.0.

Table 2. Influence of *N*-Acetylphenylalanine Equivalency of the Outcome of Enantioselective Palladation[a]

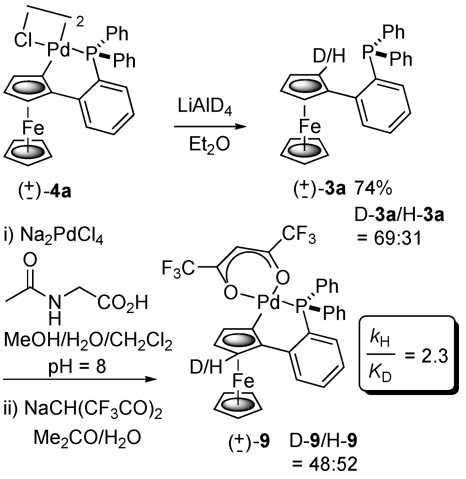
entry	substrate	amt of (*R*)-*N*-acetylphenylalanine, equiv	product/yield, %	ee, %/confign
1	**3b**	2	**4b**/81	65/$_p$*S*
2	**3b**	0.1	**4b**/10	28/$_p$*S*
3	**5**	0.1	**6**/9	95/$_p$*S*
4[b]	**5**	0.1	**6**/35	95/$_p$*S*
5[c]	**5**	0.1	**6**/51	95/$_p$*S*
6	**3b**	0	**4b**/54	
7	**5**	0	**6**/20	

[a] All reactions were performed using the standard conditions with a reaction time of 24 h unless otherwise stated. [b] With 5 equiv of NaCl. [c] With 5 equiv of LiCl.

(entry 3). The addition of 5 equiv of NaCl to promote carboxylate/chloride ligand exchange increased the yield to 35% (entry 4), and the use of 5 equiv of LiCl further increased the yield to 51% (entry 5). Again in both these cases no erosion of enantioselectivity was observed. These results suggest that dissociation of the carboxylate ligand from the product palladacycle is the factor preventing the efficient application of *N*-acetylphenylalanine as a catalyst in enantioselective palladation. As expected, in the absence of *N*-acetylphenylalanine, substrates **3b** and **5** both resulted in a reduced yield of the corresponding palladacycles (entries 6 and 7). The 54% yield obtained with **3b** suggests that competitive achiral palladation of this substrate under the reaction conditions may, at least in part, be responsible for the lower enantioselectivities observed with the phosphine substrates.

The enantioselectivities observed and the requirement for a stoichiometric quantity of *N*-acyl amino acid point to these reactions proceeding via a carboxylate coordinated metal in which this ligand is intimately involved in the palladium−carbon bond forming step.[7] An electrophilic aromatic substitution pathway (S_EAr) has been postulated as the mechanism of palladation reactions on aryl substrates,[10] and ferrocene is a reactive substrate for related S_EAr reaction pathways such as Friedel−Crafts acylation.[11] An alternative concerted metalation−deprotonation (CMD) pathway, also described as a σ-bond metathesis, has been used to rationalize the acceleration of palladation and other metalation reactions in the presence of carboxylates and other basic ligands.[12,13] A number of palladium-catalyzed direct arylation reactions have displayed intramolecular isotope effects

Scheme 4. Determination of Intramolecular Isotope Effect for the Palladation of 3a



(k_H/k_D) between 3.5 and 6.5.[12d,14] These values are inconsistent with a S_EAr mechanism for the introduction of palladium and point to the operation of an alternative CMD pathway.

To determine the intramolecular isotope effect of *N*-acetyl amino acid mediated palladation, racemic **4a**[15] was first reacted with lithium aluminum deuteride, resulting in the isolation of **3a** with a 69% deuterium incorporation, as determined by ^{1}H NMR (Scheme 4). Subsequent palladation in the presence of *N*-acetylglycine followed by conversion of the product chloride-bridged dimer into the monomeric hexafluoroacetylacetonate complex **9**, and ^{1}H NMR analysis, revealed a 48% deuterium incorporation at the 3-position of the palladacycle. The calculated k_H/k_D ratio of 2.3 reveals the involvement of C−H bond cleavage in the rate-determining step, and the outcome is consistent with the participation of the carboxylate in a CMD pathway, as represented in Figure 2. Assuming phosphine coordination to palladium, which accounts for the α (*ortho*)-regioselectivity, the reaction is constrained to palladium approach *exo* to ferrocene. This is a consequence of the conformational restriction about the ferrocenyl−aryl σ bond due to the requirement that the 2-phosphino substituent is oriented away from the metallocene. A *cis*-coordinated carboxylate ligand is then positioned to participate in proton abstraction, as is also represented in Figure 2. The success of the amino acid derived ligands may be due to the conformational restrictions in the torsions designated ψ and ϕ by analogy with peptide conformational analysis on examples such as

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(15) Prepared by acetate−chloride ligand exchange[5] following room-temperature palladation with palladium acetate; see: Roca, F. X.; Richards, C. J. *Chem. Commun.* **2003**, 3002.

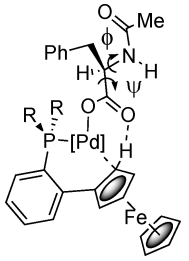

Figure 2. CMD pathway for enantioselective palladation with (*R*)-*N*-acetylphenylalanine.

Ac-ala-NHMe (the alanine dipeptide).[16] The extended β-conformation ($\varphi \approx 120$, $\phi \approx -120$) is the most stable in water,[16b] and it is of note that in this conformation the methine hydrogen of the stereogenic center is oriented toward the phosphine substituents, which may account for the preferred formation of the ($_pS$)-palladacycle. A similar model can be envisaged to account for the enantioselectivity observed with substrate **5**.

In conclusion, we have demonstrated an improvement and extension of the Sokolov procedure for the enantioselective synthesis of planar chiral ferrocene palladacycles. The use of *N*-acetylphenylalanine as a chiral carboxylic acid additive resulted in superior enantioselectivities compared to *N*-acetylleucine, and the methodology is applicable to the synthesis of scalemic phosphapalladacycles. A k_H/k_D value of 2.3 is consistent with a concerted metalation−deprotonation mechanism in which a coordinated chiral carboxylate acts as a base in the enantioselective carbon−palladium bond forming step.

Experimental Section

General Procedure for Asymmetric Palladation. A solution of the amino acid derivative (0.22 mmol) and NaOH (0.009 g, 0.22 mmol) in water (1.7 mL) was added to a solution of Na_2PdCl_4 (0.066 g, 0.22 mmol) in MeOH (5.2 mL), and the pH of the resulting solution was adjusted to 8 with 50% NaOH. A solution of the ferrocene derivative (**3a**,**b** or **5**; 0.22 mmol) in MeOH and CH_2Cl_2 (5.0 mL, typically 4:1) was added to the stirred solution, and a precipitate began to appear after ~15 min. The mixture was stirred overnight (minimum 15 h). The organic solvents were removed in vacuo, and the aqueous residue was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried ($MgSO_4$) and filtered and the solvent removed in vacuo to give the product palladacycles as either an orange-red (**4a**) or dark red crystalline solid (**4b** and **6**). The enantiomeric excess and absolute configuration of **4a**,**b** were determined as previously reported.[5] The absolute configuration of **6** was determined by polarimetry; the product of the reaction with (*R*)-*N*-acetylphenylalanine gave $[\alpha]_D^{25} = -466$ (0.08, CH_2Cl_2) (lit.[7] ($_pR$)-**6** $[\alpha]_D^{20} = +461$ (*c* 1.28, CH_2Cl_2), 68% ee).

Synthesis of 8 and the Determination of the ee of 6. A suspension of ($_pS$)-**6** (0.088 g, 0.11 mmol) in acetone (5 mL) was combined with an aqueous solution (10 mL) containing (*S*)-proline (0.083 g, 0.72 mmol) and $NaHCO_3$ (0.061 g, 0.72 mmol), and the mixture was stirred for 24 h at room temperature. The organic solvent was removed in vacuo, and the aqueous residue was extracted with CH_2Cl_2 (2 × 10 mL). The organic phase was dried ($MgSO_4$) and filtered and the solvent removed in vacuo to give the product (S,$_pS$)-**8** (0.089 g, 87%). $[\alpha]_D^{25} = -123.5$ (*c* 0.003, $CHCl_3$). A dr of 98:2 (and thus a 96% ee for **6**) was determined using the following signals in the ^{1}H NMR spectrum (δ, 400 MHz, $CDCl_3$): S,$_pS$, 2.81 (3H, s, NCH_3), 3.07 (3H, s, NCH_3), 4.12 (5H, s, C_5H_5); S,$_pR$, 2.82 (3H, s, NCH_3), 2.95 (3H, s, NCH_3), 4.23 (5H, s, C_5H_5).

Synthesis of Deuterated 3a. To a solution of **4a** (0.119 g, 0.10 mmol) in Et_2O (5 mL) was added an excess of $LiAlD_4$. The resulting mixture, which immediately turned black, was stirred at room temperature for 2 h and then quenched with H_2O (20 mL). The organic layer was separated, dried ($MgSO_4$), and evaporated in vacuo to give **3a** as a yellow solid (0.067 g, 74%). The ratio of deuterated and nondeuterated[5] **3a** was determined as 69:31. ^{1}H NMR (δ, 400 MHz, $CDCl_3$): 4.00 (5H, s, C_5H_5), 4.12 (2H, br s, β-FcH), 4.37 (1.31H, br s, α-FcH), 6.77 (1H, t, J = 8.0, Ph), 7.05 (1H, t, J = 8.0, Ph), 7.18−7.31 (11H, m, Ph), 7.83−88 (1H, m, Ph). High-resolution MS (*m*/*z*, ETD): found for MH^+ 448.1018, calcd for $C_{28}H_{23}DFeP$ 448.1022.

Palladation of Deuterated 3a and the Synthesis of 9. A solution of *N*-acetylglycine (0.008 g, 0.07 mmol) and NaOH (0.003 g, 0.07 mmol) in water (1.7 mL) was added to a solution of Na_2PdCl_4 (0.020 g, 0.07 mmol) in MeOH (5.2 mL), and then the pH of the resulting solution was adjusted to 8.0 with 50% NaOH. A solution of the deuterated **3a** (0.031 g, 0.07 mmol) in MeOH and CH_2Cl_2 (5 mL, 4:1) was added to the stirred solution, and a precipitate began to appear after ~1 h. The mixture was stirred at room temperature overnight. The organic solvents were removed in vacuo, and the aqueous residue was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried ($MgSO_4$) and filtered and the solvent removed in vacuo to give the crude palladacycle **4a**.

To the palladacycle was added sodium hexafluoroacetylacetonate (0.075 g, 0.33 mmol), acetone (5 mL), and water (3 mL). The resulting mixture was stirred vigorously at room temperature until a precipitate was formed (24 h). The organic solvent was removed in vacuo, and the aqueous residue was extracted with CH_2Cl_2 (2 × 10 mL). The organic phase was dried ($MgSO_4$), filtered, and column chromatographed (SiO_2, CH_2Cl_2) to give **9** as an orange crystalline solid (0.035 g, 66%). The ratio of deuterated and nondeuterated **9** (see the Supporting Information) was determined as 48:52.

Data for **9** are as follows. Mp: 140−145 °C. IR (NaCl): ν_{max} 1638, 1589, 1550 cm^{-1}. ^{1}H NMR (δ, 400 MHz, $CDCl_3$): 4.10 (5H, s, C_5H_5), 4.40 (1H, br s, FcH), 4.74 (1.52H, br s, FcH), 5.94 (1H, s, COCH), 6.85 (1H, t, J = 8.0, Ph), 7.03 (1H, t, J = 8.0, Ph), 7.19 (1H, t, J = 8.0, Ph), 7.29−7.37 (11 H, m, Ph), 7.45 (1H, br s, Ph). ^{13}C NMR (δ, 100 MHz, $CDCl_3$): 67.5, 70.8, 73.6, 80.0 (d, J = 35), 82.8 (d, J = 17), 89.7, 119.3, 120.2, 125.1, 125.2, 127−129, 129.5, 130.5, 131.2, 131.3, 132.0, 132.8, 134.1, 134.3, 148.7, 149.0, 175.5 (q, J = 50). ^{31}P NMR (δ, 400 MHz, $CDCl_3$): 33.29. MS (*m*/*z*, EI): 754 (4%), 755 (6), 756 (25), 757 (64), 758 (100), 759 (74), 760 (64), 761 (60), 762 (38), 763 (28), 764 (10), 765 (2).

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Supporting Information Available: Text and figures giving details of the origin of **7a**−**j**, further information on the methods of ee determination for ($_pS$)-**4a**, ($_pS$)-**4b**, and ($_pS$)-**6**, and the synthesis and characterization of ($_pS$)-H-**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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