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Novel Ferrocenyl Ligands with Planar and Central Chirality in Pd-Catalyzed Allylic Substitutions

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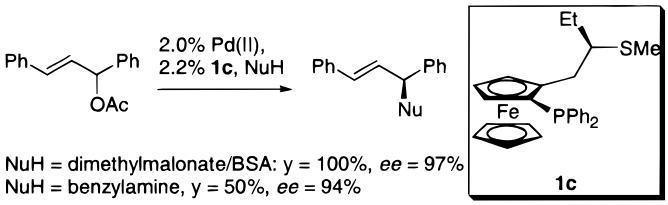
ABSTRACT



The use of planar chiral ferrocenyl ligands bearing a stereogenic center in β-position of the side chain was investigated in Pd-catalyzed enantioselective allylic substitutions. By employing 2.2 mol % of a *P,S*-ligand and 1.0 mol % of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, the alkylation of the standard test system (±)-(*E*)-diphenyl-2-propenyl acetate using dimethylmalonate/BSA as nucleophile proceeded in quantitative yield with an ee of 97%, which is the best value reported so far in this reaction using a *P,S*-ligand.

The application of planar chiral ferrocenyl ligands to asymmetric catalysis has recently received considerable interest.[3] Planar chiral ferrocenes, which additionally possess a stereocenter in α-position to the ferrocenyl moiety have shown efficiency as catalysts for asymmetric synthesis both in research and industrial processes.[4] Recently, we reported the synthesis of novel bidentate planar chiral ferrocenyl ligands of type **1** bearing a stereogenic center in β-position of the side chain.[5] All of these ligands have at least one sulfur donor group (E^1 or E^2), the second donor atom may be phosphorus, selenium, or another sulfur (Figure 1). The initial aim for synthesizing these ligands was to investigate the effect changing the position of the stereocenter from the α-to the β-position on the levels of asymmetric induction for catalytic processes.

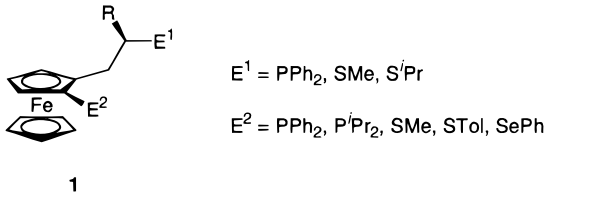


Figure 1. Novel ferrocenyl ligands **1**.

In our initial studies concerning asymmetric catalysis using the ligands **1** we concentrated on Pd-catalyzed allylic substitutions.[6] A brief screening in the standard test reaction

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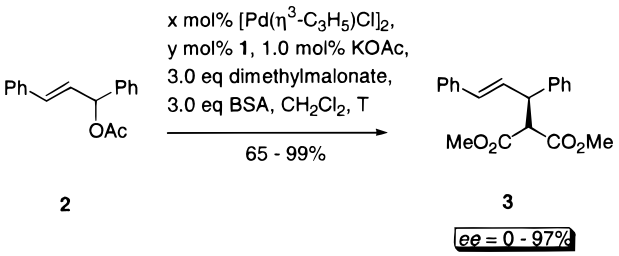
Scheme 1. Enantioselective Allylic Alkylation of **2**



2 **3**

ee = 0 - 97%

2 → **3** shown in Scheme 1 demonstrated that *S*,*S*- and *Se*,*S*-ligands **1a** and **1b** displayed low reactivity and selectivity (Table 1).

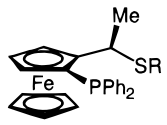
Table 1. Reaction Conditions, Yields, and Enatiomeric Excess Values in **2** → **3**

1	E^1	E^2	R	*T* (°C)	x	y	*t* (h)	yield (%)[a]	ee (%)[b]
a	S^{i}Pr	STol	Et	20	2.5	5.5	100	84	20
b	S^{i}Pr	SePh	Et	20	2.5	5.5	100	65	44
c	SMe	PPh_2	Et	20	2.5	5.5	0.16	99	90
c	SMe	PPh_2	Et	−20	1.0	2.2	24	99	97
d	SMe	PPh_2	Me	20	2.5	5.5	0.16	98	91
e	SMe	P^{i}Pr$_2$	Et	20	2.5	5.5	1	99	70
f	S^{i}Pr	PPh_2	Me	20	2.5	5.5	1	99	80
g	PPh_2	SMe	Me	20	2.5	5.5	1	99	0

a Yield of isolated **3**. *b* Determined by ^{1}H NMR ($CDCl_3$) with chiral shift reagent Eu(tfc)$_3$. (*R*) Configuration determined by the sign of optical rotation.

By employing *P*,*S*-ligands, we found a completely different situation. The Pd−π-allyl complex is enourmously activated by the phosphorus group as a strong π-acceptor. In combination with the thioether unit as a good donor and weak acceptor,[7] we have a hybrid system that allows electronic control of the nucleophilic attack to the allylic system. As is well-known, the nucleophilic attack is expected to proceed *trans* to the better π-acceptor (here the PR_2 group), since the electronic density of the allylic system is lowest at this position. This strategy has previously been successfully applied by the use of *P*,*N*-,[8] *N*,*S*-,[9] and *P*,*S*-Pd chelates.[10] When ligands **1c** and **1d** were used, the reaction proceeded quantitatively within 10 min at room temperature in CH_2Cl_2 (*y* = 99 and 98%), yielding the product with an enantiomeric excess of 90 and 91%. By changing the PPh_2 group of **1c** to the P^{i}Pr$_2$ group (ligand **1e**), the ee was lowered from 90 to 70%, probably partly owing to the P^{i}Pr$_2$ moiety being a weaker π-acceptor leading to a decrease in regioselectivity of the nucleophilic attack. The observed results indicate, that the steric control also has to be fine-tuned. Since nucleophilic attack is preferred *cis* to the *S*-donor group, this should be even more favorable the smaller the thioether unit is. Changing the SMe group of **1d** to the S^{i}Pr group (ligand **1f**) decreases the ee from 91 to 80%. The steric influence is demonstrated with *P*,*S*-ligand **1g**, which yields the racemic product, since the thioether group is connected to the bulky ferrocenyl core.

Owing to the high reactivity of the Pd−allyl complexes with ligands **1c** and **1d**, it was possible to run the reaction at −20 °C to enhance the stereoselectivity. Subsequently, we concentrated on ligand **1c**, despite **1d** giving slightly better results, since the former can be obtained in much higher yields and it is far less air sensitive. The extraordinary air sensitivity of **1d** is quite surprising, as the structural difference between **1c** and **1d** is very small. The product could be isolated in quantitative yield and with an ee of 97% by simultaneous decrease of the amount of catalyst from *x* = 2.5 to *x* = 1.0 mol % (*y* = 2.2 mol % **1c**).[11] The high selectivities are noteworthy, since ligands **4** bearing the



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stereogenic center in α-position yield the product with an ee of only 34% (R = ethyl) or 67% (R = cyclohexyl). By changing the alkyl group of the sulfur donor atom to a chiral sugar moiety an ee of 88% was reached.[10c]

To the best of our knowledge, an enantiomeric excess of 97% is the best value in this reaction so far reported for a *P*,*S*-ligand. Compared to *N*,*S*-ligands, *P*,*S*-ligands have the

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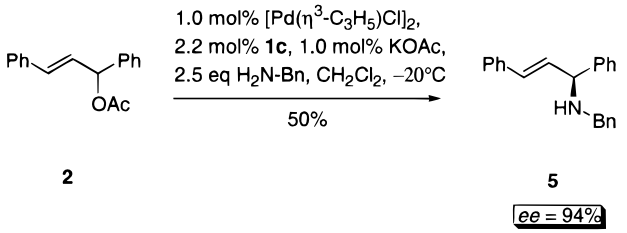
(11) A mixture of (π-allyl)palladium chloride dimer (3.7 mg, 0.01 mmol) and ligand **1c** (10.4 mg, 0.022 mmol) in 1.5 mL CH_2Cl_2 was stirred at room temperature for 1 h. The solution was cooled to −20 °C and 1.0 mmol of acetate **2** (252 mg) in 0.5 mL of CH_2Cl_2 was added, followed by the nucleophile [alkylation: 3.0 mmol dimethylmalonate (0.34 mL) and 3.0 mmol *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 0.74 mL); amination: 2.5 mmol benzylamine (0.27 mL)] and KOAc (1.0 mg, 0.01 mmol) sequentially. After completion (TLC analysis) or after a certain time elapsed, the reaction mixture was diluted with 20 mL of Et_2O, quenched with 20 mL of saturated aqueous NH_4Cl, and washed with 20 mL of saturated brine. The organic layer was dried over $MgSO_4$. After evaporation of the solvent in vacuo, the crude product was purified by column chromatography (eluant: 20% diethyl ether in hexane).

advantage of higher reactivity and therefore much shorter reaction times.

A similar temperature effect as for the alkylation noted before was found for the amination reaction using benzylamine as nucleophile (Scheme 2).

Scheme 2. Enantioselective Allylic Amination of **2**



2 **5**

ee = 94%

Reducing the reaction temperature from +20 °C to −20 °C increases the ee of **5** from 84 to 94% [(*S*) configuration]. However, this higher selectivity was accompanied by a decrease in yield from 93 to 50%.[11]

For $CDCl_3$ solutions of complex **6**[12] we observed four isomers in the ratio 86:9:3:2 with ^{31}P NMR chemical shifts of δ = 15.2, 14.9, 17.8, and 21.1 ppm, respectively. The configuration of the major isomer was unambiguously determined to be *exo-syn-syn* (*exo* refers to the relative orientation of the central allylic C−H vector pointing away from the ferrocenyl core; substituents on allylic ligands are named according to their configuration relative to the central C−H bond) by ^1H NMR-NOE experiments (Figure 2).

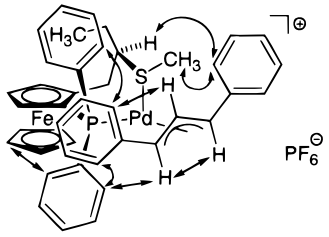


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Figure 2. NOE connectivities of **6**.

The ^{13}C NMR chemical shifts for the allyl terminus *trans* to phosphorus δ = 102.5 ppm and *trans* to sulfur δ = 78.2 ppm indicate that the carbon *trans* to phosphorus should be much more electrophilic thus allowing a regiocontrol of the nucleophilic attack. On the basis of the plausible assumption that (*R*)-**3** and (*S*)-**5** result from preferential attack on this major *exo-syn-syn* isomer, then the nucleophilic attack proceeds as expected *trans* to phosphorus.

The solid-state structure also reveals the *exo-syn-syn* geometry with pseudo square-planar coordination around palladium (Figure 3). The 1,3-diphenylallyl ligand is rotated

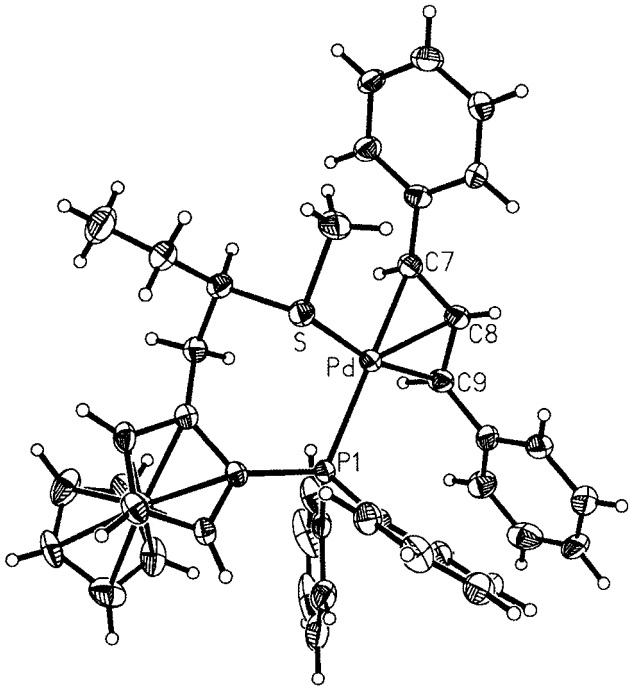

Figure 3. Absolute configuration of **6** (without anion and solvent) with 50% probability displacement ellipsoids. Selected bond lengths are as follows: Pd−S = 2.400(1), Pd−P1 = 2.326(1), Pd−C7 = 2.274(5), Pd−C8 = 2.188(4), Pd−C9 = 2.176(4), C7−C8 = 1.384(6), and C8−C9 = 1.404(6) Å.

in a clockwise manner along the Pd−allyl axis so that the terminal allyl carbon *trans* to phosphorus (C-7) is found to be 0.447 Å below the P−Pd−S coordination plane (C(8) and C(9) are 0.450 and 0.136 Å above this plane). As expected, the Pd−C bond lengths are significantly different, with the carbon atom *trans* to phosphorus having the longer distance (Pd−C(7) = 2.274(5) Å) compared to the one *trans* to sulfur (Pd−C(9) = 2.176(4) Å), indicating the higher *trans* influence of the phosphino moiety. The plane of the allyl fragment is tilted 22.8° from the perpendicular to the P−Pd−S coordination plane.[13]

In conclusion, the studies presented demonstrate that planar chiral ferrocenyl ligands bearing a stereocenter in β-position

(12) **Preparation of 6.** A total of 38 mg of bis[μ-chloro(η^3-PhCHCHCHPh)palladium(II)] (0.056 mmol) was added to a solution of 53 mg of ligand **1c** (0.112 mmol) in 10 mL of acetone. After 30 min of stirring at room temperature, 39 mg of $TlPF_6$ (0.112 mmol) was added. After 1 h, the mixture was decanted and TlCl filtered off over Celite. The solution was concentrated to one-quarter under a stream of argon and 30 mL of *n*-pentane were added causing oiling out of a dark red material. The pure compound was obtained in 97% yield after crystallization from CH_2Cl_2/Et_2O at −26 °C.

(13) **X-ray Data for 6.** $C_{42}H_{42}FePPdS^+ \cdot PF_6^- \cdot CH_2Cl_2$; M_r = 1001.93; orthorhombic, $P2_12_12_1$; a = 10.239(1), b = 19.986(4), c = 20.559(3) Å; V = 4207(1) Å^3; Z = 4; D_x = 1.582 g cm^{-3}; μ(Mo Kα) = 1.083 mm^{-1}; 147 K. Structure refinement with SHELXL-97; H atoms riding; final R = 0.061 for 9445 observed reflections. Crystallographic data (without structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-135357. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax +44 1223 336033 or e-mail deposit@ccdc.cam.ac.uk).

of the side chain, may be superior in certain catalytic reactions in comparison to α-functionalized ferrocenes.

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