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MODIFICATION OF OPTICALLY ACTIVE FERROCENYLPHOSPHINE LIGANDS FOR PALLADIUM-CATALYZED ASYMMETRIC ALLYLIC ALKYLATION

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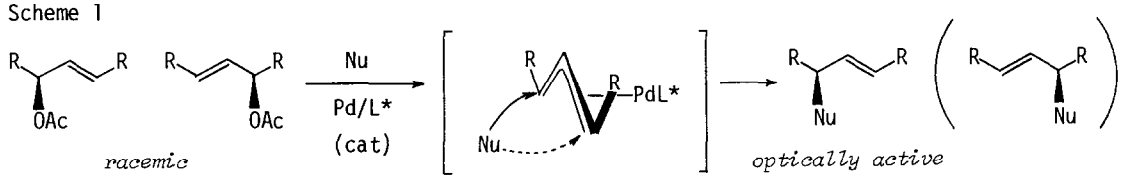
Summary: Optically active ferrocenylphosphines containing a functional group on the side chain were effective as ligands for the palladium-catalyzed asymmetric allylic alkylation of 1,3-disubstituted allyl acetates such as 1,3-diphenyl-3-acetoxy-1-propene with sodium acetylacetonate and related soft carbon nucleophiles to give the alkylation products of up to 92% ee.

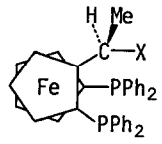
In recent years, asymmetric carbon-carbon bond forming reactions catalyzed by transition-metal complexes containing optically active phosphine ligands have been the subjects of increased research activity.[1] One of the most interesting and challenging problems in research on the catalytic asymmetric synthesis is development of the ligand which will fit in with a given reaction as efficiently in stereoselectivity as possible. Chiral ferrocenylphosphines have been demonstrated to be superior to others in that structural modification can be readily made by introduction of a desired functional group on the side chain according to the demand of the reaction type.[2]

Here we report the use of chiral ferrocenylphosphine ligands for palladium-catalyzed asymmetric alkylation of racemic 1,3-disubstituted allyl acetates, where the π-allylpalladium intermediate containing an achiral π-allyl group results from both enantiomers of the allyl substrate and the asymmetric induction arises from a preferential attack by the nucleophile on either of the two diastereotopic π-allyl carbon atoms in the intermediate (Scheme 1).[3,4,5]

Scheme 1



Studies on stereochemistry of the allylic alkylation have revealed that soft carbon nucleophiles represented by sodium dimethyl malonate attack the π-allyl carbon from the side opposite to the palladium.[6,7] On the basis of the mechanism, the functional groups which are expected to interact with the incoming nucleophile to bring about high stereoselectivity (Figure 1), were introduced at the side chain of chiral ferrocenylphosphines. Thus, the ferrocenylphosphines **1a**, **1b**, and **1c** were prepared from (R)-1-[(S)-1',2-bis(diphenylphosphino)-ferrocenyl]ethyl acetate.[8]



(*R*)-(*S*)-BPPF-X

1a: X = NMe(CH2OH)(CH2OH)

1b: X = N(CH2OH)(CH2OH)

1c: X = NMe(CH2OH)

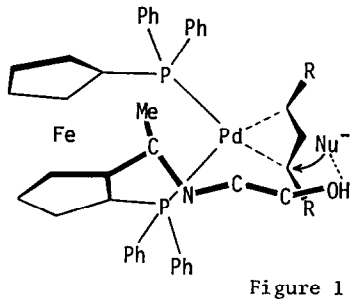
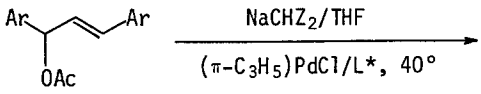


Figure 1

The ferrocenylphosphines were examined for stereoselectivity in the reaction of racemic (E)-1,3-diphenyl-3-acetoxy-1-propene (**3**) with sodium acetylacetonate in THF (eq 1). The reaction conditions and results are summarized in Table 1, which also contains data obtained with other phosphine ligands for comparison.



dl-**3**: Ar = Ph

dl-**4**: Ar = 1-Np

5a-d: Ar = Ph

6a: Ar = 1-Np

CHZ2

a: $CH(COMe)_2$

b: CH(COMe)COPh

c: CH(COMe)COOMe

d: $CH(COOMe)_2$ (1)

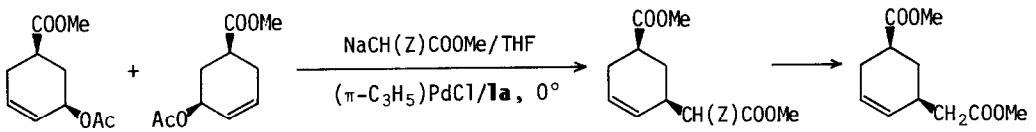
The highest stereoselectivity was obtained in the reaction with the ferrocenylphosphine containing N-methyl-N-bis(hydroxymethyl)methylamino group (**1a**), which gave (S)-(E)-1,3-diphenyl-2-propenylacetylacetone (**5a**) of 90% ee in a quantitative yield (entry 1). In the reaction of (E)-1,3-di(1-naphthyl)-3-acetoxy-1-propene (**4**) the enantiomeric purity of the alkylation product **6a** was 92% (entry 2). The ferrocenylphosphines **1b** and **1c** which have 2-hydroxyethyl group(s) on the amino side chain were also effective in producing (S)-(E)-**5a** of over 70% ee (entries 3 and 4). The stereoselectivity achieved here is among the highest for the catalytic asymmetric carbon-carbon bond forming reactions.[1] Lower selectivity was observed in the reaction with the ligands **2a**, **2b**, and **2c**, which are the ferrocenylphosphines lacking the hydroxy group (entries 5, 6 and 7). It is probable that the hydroxy groups on the ligand **1a**, **1b**, or **1c**, which are located outside the π-allyl of the π-allylpalladium intermediate, interact attractively with the acetylacetonate by hydrogen bonding as shown in Figure 1, and the interaction is responsible for the high stereoselectivity, controlling the attack of the nucleophile on the π-allyl carbon. Introduction of the hydroxy group at the ferrocenylmethyl position in the ligand **2d** brought about the reversal of the stereocontrol to give (R)-**5a** of 46% ee (entry 8). The use of (-)-DIOP[9] or BPPM[10] resulted in the formation of almost racemic product **5a** (entries 9 and 10). The inefficiency of these ligands is ascribed to the lack of functional groups which can interact with the nucleophile. Sodium salts of benzoylacetone and methyl acetoacetate were also successfully used for the asymmetric alkylation of **3** to give the corresponding products **5b** and **5c** with (S) configuration of 87% and 83% ee, respectively (entries 11 and 12). The absolute configuration of **5a-d** was correlated[11] with that of dimethyl (S)-(+)-2-phenylsuccinate[12] and their enantiomeric purity was determined by ^{1}H NMR spectroscopy using the chiral shift reagent $Eu(hfc)_3$ or $Eu(dcm)_3$.[13]

Table 1. Asymmetric Allylic Alkylation of (E)-1,3-Diphenyl-3-acetoxy-1-propene (3) Catalyzed by Chiral Ferrocenylphosphine-Palladium Complexes.[a]

entry	-X in (R)-(S)-BPPF-X	nucleophile	product	yield[b](%)	% ee[c](confign)
1	-NMeCH(CH_2OH)$_2$ (**1a**)	NaCH($COMe$)$_2$	**5a**	97	90[d] (S)
2[e]	-NMeCH(CH_2OH)$_2$ (**1a**)		**6a**	40	92[f]
3	-N(CH_2CH_2OH)$_2$ (**1b**)		**5a**	86	81 (S)
4	-NMeCH_2CH_2OH (**1c**)		**5a**	86	71 (S)
5	-NMe_2 (BPPFA, **2a**)		**5a**	51	62 (S)
6	-N-(CH_2)$_5$ (**2b**)		**5a**	90	44 (S)
7	-Me (**2c**)		**5a**	92	10 (R)
8	-OH (BPPFOH, **2d**)		**5a**	26	46 (R)
9	(-)-DIOP[g]		**5a**	88	0
10	BPPM[h]		**5a**	86	7 (R)
11	-NMeCH(CH_2OH)$_2$ (**1a**)	NaCH($COMe$)$COPh$	**5b**	93	87[i] (S)
12	-NMeCH(CH_2OH)$_2$ (**1a**)	NaCH($COMe$)$COOMe$	**5c**	96	83[j] (S)
13	-NMeCH(CH_2OH)$_2$ (**1a**)	NaCH($COOMe$)$_2$	**5d**	98	48[k] (S)

[a] To a mixture of a ligand (0.011 mmol), di-μ-chlorobis(π-allyl)dipalladium (0.005 mmol), and the acetate **3** (1.0 mmol) in THF (5 ml) was added a suspension of sodium enolate prepared from sodium hydride (1.2 mmol) and acetylacetone or a related active methylene compound (1.5 mmol) in THF (5 ml) at room temperature. The mixture was stirred at 40°C for 13-19 hr. After hydrolysis and the usual work-up, the product was isolated by preparative TLC on silica gel (hexane/ethyl acetate = 5/1). [b] Isolated yield. [c] Determined by ^{1}H NMR using Eu(hfc)$_3$ or Eu(dcm)$_3$. [d] The rotation of **5a** was $[\alpha]_D^{20}$ +14.9° (c 1.8, ethanol). [e] Reaction of racemic (E)-1,3-di(1-naphthyl)-3-acetoxy-1-propene (**4**). [f] $[\alpha]_D^{20}$ -90.7° (c 1.2, ethanol). [g] (-)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane. [h] (2S,4S)-N-t-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine. [i,j,k] The rotations of **5b**, **5c**, and **5d** were $[\alpha]_D^{20}$ -15.6°, -2.4°, and -5.2° (c 1.4-1.8, ethanol), respectively.

The high efficiency of the palladium catalyst coordinated with the ferrocenylphosphine **1a** was also observed in the reaction of cyclic acetate **7**, which gave the alkylation products (R,R)-**8a** and -**8b** of over 70% ee (eq 2).[14]



(2)

dl-**7**

Z = COMe: 97% (*R*,*R*)-**8a**, 71% ee

Z = COOMe: 95% (*R*,*R*)-**8b**, 72% ee

(*S*,*S*)-**9**

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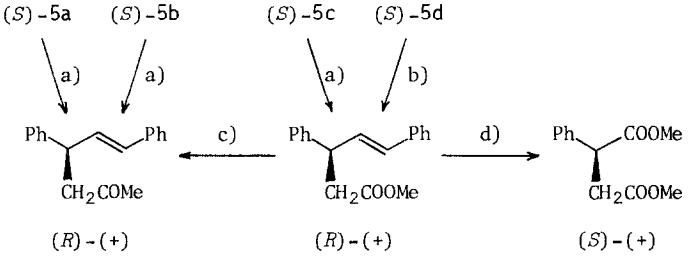
11 The following transformations were carried out:



a) NaOMe/MeOH, reflux
b) NaCN/LiI/DMF, 120°
c) 1. $Cp_2TiCH_2ClAlMe_2$/THF
2. aq.HCl/THF
d) 1. $KMnO_4/NaIO_4$
2. CH_2N_2/THF

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14 Enantiomeric purity was determined by ^1H NMR of (S,S)-(+)-**9**[3a] using $Eu(dcm)_3$.[13]

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