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Asymmetric Allylic Alkylation of 1,3-Disubstituted 2-Propenyl Acetates Catalyzed by a Chiral Ferrocenylphosphine-Palladium Complex

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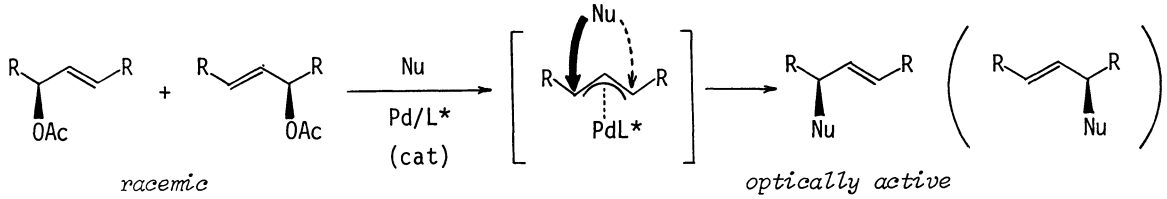
Reaction of racemic 2-propenyl acetates substituted with two different aryl groups at 1 and 3 positions with sodium acetylacetonate in the presence of a palladium catalyst containing an optically active ferrocenylphosphine ligand gave regioisomeric allylic alkylation products of high optical purity (up to 95% ee).

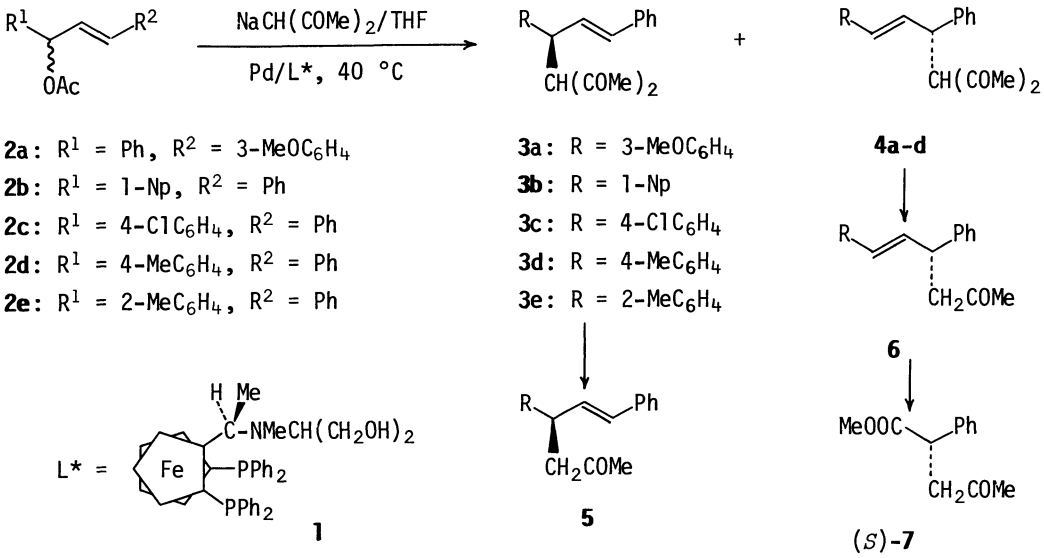
We have previously reported[1] that the optically active ferrocenylphosphine containing a dihydroxyalkyl group on the side chain, (R)-N-methyl-N-bis(hydroxymethyl)methyl-1-[(S)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine (**1**), is an effective ligand for the palladium-catalyzed asymmetric allylic alkylation of racemic 2-propenyl acetates such as 1,3-diphenyl-3-acetoxy-1-propene which have the same substituent groups at 1 and 3 positions. The reaction proceeds via the π-allylpalladium intermediate containing a meso type π-allyl group and the asymmetric induction arises from preferential attack by a soft carbon nucleophile on either of the diastereotopic π-allyl carbon atoms (Scheme 1). Here we report the



Scheme 1.

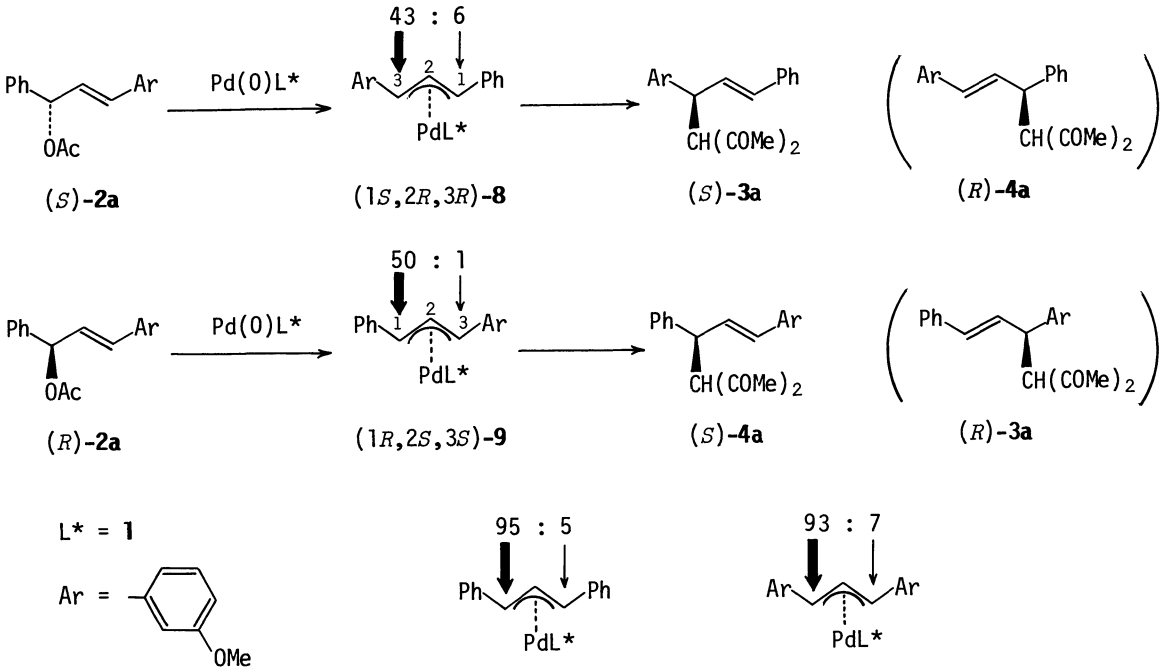
results obtained for the asymmetric allylic alkylation of racemic 2-propenyl acetates substituted with two different groups at 1 and 3 positions which should include chiral π-allylpalladium complex in the catalytic cycle.

Racemic (E)-1-(3-methoxyphenyl)-3-phenyl-3-acetoxy-1-propene (**2a**) was allowed to react with sodium acetylacetonate in THF at 40 °C for 45 h in the presence of 1 mol% of the palladium catalyst prepared in situ by mixing di-μ-chlorobis(π-allyl)dipalladium with the chiral ferrocenylphosphine **1**.[1,2] Aqueous workup followed by preparative TLC on silica gel (hexane/ethyl acetate = 5/1) gave 92% yield of allylic alkylation products consisting of [(E)-styryl]-(3-methoxyphenyl)methylacetylacetone (**3a**) and its regioisomer **4a** in a ratio of 44/56. Deacetylation of the products with sodium methoxide in refluxing methanol gave methylketones **5a** and



6a, the enantiomeric purities of which were estimated to be 95% ee and 81% ee, respectively, by ^{1}H NMR in the presence of a chiral shift reagent Eu(hfc)$_3$[3] (entry 1 in Table 1). Thus, both of the regioisomeric alkylation products 3a and **4a** have been found to have the enantiomeric purities of over 80% ee. The absolute configuration of 4a was determined to be (S) by converting it into (S)-ketoester **7**.[4] It is assumed that the configuration of the regioisomer **3a** was also (S) since the stereochemistry of the catalytic alkylation has been established to be retention of configuration[5,6] (vide infra).

The stereochemical results can be visualized by Scheme 2. Oxidative addition



Scheme 2.

Table 1. Asymmetric Allylic Alkylation of 1,3-Disubstituted 2-Propenyl Acetates with Sodium Acetylacetonate Catalyzed by a Chiral Ferrocenylphosphine-Palladium Complex[a)]

Entry	Acetate **2**[b)]	Reaction time/h	Yield[c)]/% of **3** and **4**	Ratio[d)] of **3**/**4**	% ee[e)] of **3**	% ee[e)] of **4**
1	PhCH(OAc)CH=CH(3-$MeOC_6H_4$) (**2a**)	45	92	44/56	95 (S)	80 (S)
2[f)]	PhCH(OAc)CH=CHPh	13	97		90 (S)	
3	3-$MeOC_6H_4$CH(OAc)CH=CH(3-$MeOC_6H_4$)	39	80		86	
4	1-NpCH(OAc)CH=CHPh (**2b**)	16	72	46/54	94	75
5	4-ClC_6H_4CH(OAc)CH=CHPh (**2c**)	14	73	46/54	87	70
6	4-MeC_6H_4CH(OAc)CH=CHPh (**2d**)	3	76	45/55	86	72
7	2-MeC_6H_4CH(OAc)CH=CHPh (**2e**)	21	66	31/69	80	24

a) To a mixture of the chiral phosphine **1** (0.0055 mmol), di-μ-chlorobis(π-allyl)dipalladium (0.0025 mmol), and the acetate **2** (0.5 mmol) in THF (2 ml) was added a suspension of sodium enolate prepared from sodium hydride (0.63 mmol) and acetylacetone (0.75 mmol) in THF (2 ml) at room temperature. The mixture was stirred at 40 °C. After hydrolysis and the usual work-up, the product was isolated by preparative TLC on silica gel (hexane/ethyl acetate = 5/1). b) All racemic E isomers. c) Isolated yield. d) Determined by ^{1}H NMR. e) Determined by ^{1}H NMR of **5** and **6** using Eu(hfc)$_3$. f) This result has been published (Ref. 1).

of (S)-2a to a chiral phosphine-palladium(0) species with inversion of configuration at the allylic carbon[7)] will form π-allylpalladium complex **8** which has (1S,2R,3R)-1-phenyl-3-(3-methoxyphenyl)-π-allyl group, and the diastereomeric π-allylpalladium complex **9**, which has the π-allyl group of opposite configuration (1R,2S,3S), will be formed from (R)-2a. The nucleophilic attack on C-1 carbon of π-allylpalladium complexes **8** and **9** will produce (R)-**4a** and (S)-**4a**, respectively, and that on C-3 carbon of **8** and **9** will produce (S)-3a and (R)-3a, respectively, since the soft carbon nucleophiles including acetylacetonate anion have been demonstrated to attack the π-allyl carbon from the side opposite to palladium.[6,8)] The results obtained above that the reaction of racemic **2a** gave (S)-**3a** of 95% ee and (S)-**4a** of 80% ee in a ratio of 44/56 indicate that the products consist of (S)-**3a** (43%), (R)-**3a** (1%), (S)-**4a** (50%), and (R)-**4a** (6%). The ratios of the nucleophilic attack on the π-allyl carbons are calculated to be C-1/C-3 = 6/43 for **8** and 50/1 for **9**. The chiral ferrocenylphosphine **1** is an effective ligand for the

reaction of allyl acetates which proceeds via π-allylpalladium intermediate bearing meso π-allyl fragment,[1] and it has been observed that the ratios of the nucleophilic attack on the diastereotopic π-allyl carbons of palladium intermediates complexed with **1** are 95/5 for 1,3-diphenyl-π-allyl and 93/7 for 1,3-di(3-methoxyphenyl)-π-allyl (entries 2 and 3). The ratio of the nucleophilic attack is changed to 43/6 in **8** and 50/1 in **9** by steric factors of phenyl and 3-methoxyphenyl groups.[9] The π-allyl carbon substituted with phenyl is more subject to the nucleophilic attack than that with 3-methoxyphenyl.

The asymmetric reaction of allyl acetates substituted with phenyl and several other aryl groups, 1-naphthyl (**2b**), 4-chlorophenyl (**2c**), 4-methylphenyl (**2d**), and 2-methylphenyl (**2e**), was also carried out under the similar conditions. The results summarized in Table 1 show that both of the regioisomeric alkylation products in entries 4-6 were obtained with high enantiomeric purity (>70% ee) and the minor regioisomers **3** always had higher % ee values than the major ones as can be expected from the reaction mechanism. It should be noted that the regioselectivity of nucleophilic attack was not strongly dependent on the electronic nature of the aryl group, the ratio of **3**/**4** being between 44/56 and 46/54 in the reaction of acetates containing 3-methoxyphenyl (**2a**), 4-chlorophenyl (**2c**), and 4-methylphenyl (**2d**) (entries 1, 5, and 6). The regioselectivity seems to be controlled mainly by the steric bulkiness of the aryl substituents in all cases encountered.

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