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PALLADIUM-CATALYZED ASYMMETRIC ALKYLATION VIA Π-ALLYL INTERMEDIATE : ACETAMIDOMALONATE ESTER AS A NUCLEOPHILE.

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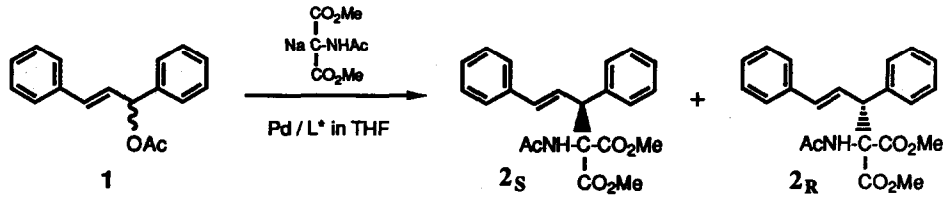
Summary: Asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with sodium salt of acetamidomalonate ester has been carried out in the presence of a palladium catalyst containing (*S*)-BINAP to give a chiral α-allyl-α-acetamidomalonate ester derivative of high optical purity (94±1% ee).

Asymmetric allylic alkylation reaction catalyzed by π-allylpalladium complex is a useful synthetic tool for asymmetric carbon-carbon bond formation.[1] As for enantioselective reaction through a symmetrical π-allyl intermediate, moderate or high enantiomeric excess was reported by Trost et al. (up to 68%)[2] and Hayashi et al. (up to 96%).[3,4] Though chiral ligands bearing bulky substituents such as trimethylsilyl groups or a side arm with functional groups such as hydroxyl groups were successfully employed in those reactions, relatively simple ligands, for example (*S*)-BINAP, failed to show high enantioselectivity.[1,2] Here we report that remarkable improvement on enantioselectivity in allylic alkylation reaction was achieved by using tertiary carbanion derived from acetamidomalonate ester as a nucleophile instead of secondary carbanion (scheme 1). To the best of our knowledge, it is for the first time that the acetamidomalonate ester was employed as a nucleophile in asymmetric allylic alkylation.[5]



scheme 1

The allylic alkylation reactions of 1,3-diphenyl-2-propenyl acetate (1) with the sodium salt of dimethyl acetamidomalonate were carried out in the

presence of $[(\pi\text{-}C_3H_5)PdCl]_2$ and chiral diphosphine. The reaction conditions and the results are summarized in Table 1. The product (2) was obtained in high yield after column chromatographic purification.[6] Enantiomeric excess of the product was determined by its ^1H NMR spectra using the chiral shift reagent, $[Eu(hfc)_3]$, and HPLC analysis using a chiral column. Data obtained by both methods agreed well within 1-4%.

Table 1 shows that the Pd/ligand ratio affected enantioselectivity (entry 1-7). With (*S*)-BINAP and (*S,S*)-chiraphos the maximal selectivity was obtained when Pd/ligand ratio was 1.2. The highest enantiomeric excess obtained was 94±1% with (*S*)-BINAP (entry 1). The chiral ligands possessing C_2-symmetry, such as (*S*)-BINAP, (*S,S*)-Norphos, and (*S,S*)-chiraphos, showed high selectivity. The absolute configuration of the major product was proved to be *S* by the comparison with the authentic sample derived from $3_R(+)$ as shown in scheme 2.[3,7]

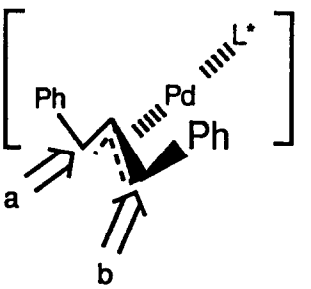
Table 1. Palladium-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl acetamidomalonate[a]

entry	chiral ligand[b]	Nu (X=)[f]	L*/Pd	time (h)	yield[c] (%)	% ee[d](configuration)[e] NMR	HPLC
1	(*S*)-BINAP	AcNH	1.2	120	92	95(*S*)	94(*S*)
2	(*S*)-BINAP	AcNH	1.1	114	84	93(*S*)	94(*S*)
3	(*S,S*)-chiraphos	AcNH	1.2	236	98	91(*S*)	86(*S*)
4	(*S,S*)-chiraphos	AcNH	1.1	151	84	75(*S*)	78(*S*)
5	(*S,S*)-Norphos	AcNH	1.2	126	89	79(*S*)	84(*S*)
6	(*S,S*)-Norphos	AcNH	1.1	67	85	83(*S*)	86(*S*)
7	(*S,S*)-Norphos	AcNH	1.5	115	84	79(*S*)	77(*S*)
8	(*S*)-(*R*)-BPPFA	AcNH	1.2	97	79	52(*S*)	55(*S*)
9	(*S,S*)-BPPM	AcNH	1.2	215	85	8(*S*)	16(*S*)
10[g]	(*S*)-BINAP	H	1.2	44	80	34(*R*)	—
11[g]	(*S*)-(*R*)-BPPFA	H	1.5	90	82	35(*R*)	—

a The chiral ligand (0.012 mmol), 1,3-diphenyl-2-propenyl acetate (1mmol), and $[(\pi\text{-}C_3H_5)PdCl]_2$ (0.005 mmol: ligand/Pd ratio is 1.2) were dissolved in THF (4 ml) at 0 °C. To a stirred suspension of sodium salt of dimethyl acetamidomalonate prepared from sodium hydride (1.2 mmol) and the ester (1.5 mmol) in THF (4 ml) at 25 °C was added the above mixture, then the mixture was stirred at 25 °C under nitrogen. After hydrolysis and the usual work-up, the product was isolated by flash chromatography on silica gel (hexane/ethyl acetate = 1/1). *b* See note 8. *c* Isolated yield. *d* Determined by ^1H NMR using $Eu(hfc)_3$ or HPLC equipped with a chiral column (CHIRALCEL OJ (DAICEL Chem. Ind. Co.), hexane/2-propanol/diethylamine = 800/200/1). *e* See text. *f* Nu = $XC(CO_2Me)_2$. *g* The same procedure except that dimethyl malonate was employed in place of dimethyl acetamidomalonate.

It is noteworthy that the displacement of the α-methyne proton of dimethyl malonate with the acetamido group enhances the enantioselectivity, as compared with the result of dimethyl malonate (entry 10-11). The enantiomeric excess attained with the tertiary carbanion derived from dimethyl acetamidomalonate is higher than that with the secondary carbanion derived from dimethyl malonate.

Soft carbon nucleophiles, such as sodium dimethyl malonate, attack the π-allylpalladium intermediate from the side opposite to the palladium atom.[4,10] The absolute configuration of the product depends on the position of the nucleophilic attack to the π-allyl moiety. As shown in scheme 3, the attack on the site *a* produces 2_R and on the site *b* produces 2_S. The results obtained here show that the nucleophile attacks the site *b* predominantly to produce the main product, 2_S.



scheme 3

As for the palladium-catalyzed asymmetric allylic alkylation, high enantioselectivity with relatively simple chiral diphosphines, such as (*S*)-BINAP, (*S,S*)-chiraphos, and (*S,S*)-Norphos was achieved for the first time. The enantiomeric excess obtained here competes with the highest one for the catalytic asymmetric carbon-carbon bond formation reactions, and is the highest for the asymmetric allylic alkylation reaction with the malonate derivatives. A single recrystallization from cyclohexane-chloroform gave optically pure product, 2_S.[11] The product, α-allyl-α-acetamidomalonate ester derivative, is a useful intermediate for the synthesis of naturally unavailable α-amino acids.[12] Further investigations with various nucleophiles are in progress.

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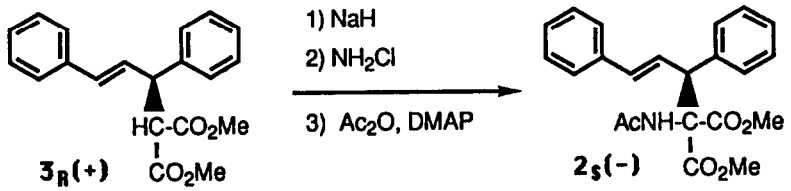
4) Hayashi, T. *Pure Appl. Chem.* **1988**, *60*, 7.

5) For the palladium-catalyzed synthesis of the α-allyl-α-acetamidomalonate ester, see: Haudegond, J-P.; Chauvin, Y.; Commereuc, D.; *J. Org. Chem.*

1979, *44*, 3063.

6) Spectral data for 2. FAB MS: 382(M+1). ^{1}H NMR: δ(ppm) 1.9(s, 3H, $C\underline{H}_3CO$), 3.6(s, 3H, $OC\underline{H}_3$), 3.8(s, 3H, $OC\underline{H}_3$), 4.73(dd, J = 6.6 and 0.9 Hz, 1H, C$\underline{H}$), 6.32(dd, J = 0.9 and 16.7 Hz, 1H, C$\underline{H}$=CH), 6.75(dd, J = 6.6 and 16.7 Hz, 1H, CH=C$\underline{H}$), 7.3(s(broad), 11H, Ph + N$\underline{H}$). ^{13}C NMR: δ(ppm) 22.8($\underline{C}H_3CO$), 53.0-($CO_2\underline{C}H_3$), 53.2(CH=CH-$\underline{C}$), 68.9(AcNH-$\underline{C}$), 126-138(Ph + $\underline{C}$H=$\underline{C}$H), 167.3, 167.6, 169.0($\underline{C}O_2Me$ + $CH_3\underline{C}O$).

7) The optical purities of the starting material 3_R and the product 2_S were 64% and 55%, respectively. $[\alpha]_D^{28}$. 3_R(+): +8.3° (c = 0.6, EtOH). 2_S(-): -24° (c = 0.6, EtOH). The optical rotation of 3_S(-) (48% ee) has been reported: $[\alpha]_D^{20}$. -5.2° (c = 1.4-1.8, EtOH).[3]



scheme 2

8) Abbreviations of the chiral ligands: (*S*,*S*)-chiraphos = (*S*,*S*)-2,3-bis(diphenylphosphino)butane.[9a] (*S*,*S*)-Norphos = (*S*,*S*)-2,3-bis(diphenylphosphino)-bicyclo[2.2.1]hept-5-ene.[9b] (*S*)-BINAP = (*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene.[9c] (*S*)-(*R*)-BPPFA = (*S*)-N,N-dimethyl-1-[(*R*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine.[9d] (*S*,*S*)-BPPM = (2*S*,4*S*)-N-(t-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine.[9e]

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10) Hayashi, T.; Konishi, M.; Kumada, M. *J. Chem. Soc., Chem. Commun.* **1984**, 107.

11) $[\alpha]_D^{20}$ = -54° (c= 0.6, EtOH). Optical purity was >99.9% by HPLC analysis.

12) For reviews including the syntheses of naturally unavailable α-amino acids, see: Williams, R. M. *Synthesis of Optically Active α-Amino Acids*, Pergamon Press, Oxford, 1989.

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