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PALLADIUM-CATALYZED ASYMMETRIC ALLYLIC ALKYLATION USING DIMETHYL MALONATE AND ITS DERIVATIVES AS NUCLEOPHILE

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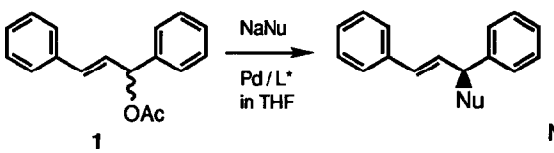
Abstract : Palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with sodium salt of dimethyl malonate and its derivatives has been successfully carried out in the presence of optically active diphosphine, such as (S)-BINAP. High enantioselectivity of up to 90% ee was obtained with dimethyl malonate.

Recently, asymmetric carbon-carbon bond formation reaction catalyzed by π-allylpalladium complex is a focus of active studies.[1] It has been shown that the enantioselectivity in the reaction depended on not only the phosphine ligand but also the nucleophile. Hayashi and coworkers have reported the excellent results (96% ee) of palladium-catalyzed asymmetric allylic alkylations using acetylacetone as a nucleophile, while the similar reaction using dimethyl malonate as a nucleophile gave only modest selectivity (46% ee).[2,3] We have previously reported that high enantioselectivity (up to 94% ee) was achieved on palladium-catalyzed asymmetric allylic alkylation with sodium salt of dimethyl acetamidomalonate.[4] Although malonate derivatives are useful intermediate in organic syntheses, high enantioselectivity has not been obtained with malonate ester in the asymmetric allylic alkylation, thus far, and the effect of the α-substituent of the malonate as a nucleophile has not been investigated. We report here the studies of palladium-catalyzed asymmetric allylic



1

Nu = $-\overset{\overset{X}{|}}{\underset{\underset{X}{|}}{C}}-R$

2 : X = CO_2Me ; R = H
3 : X = CO_2Me ; R = CH_3
4 : X = CO_2Me ; R = CH_2Ph
5 : X = CO_2Me ; R = $NHCOCH_3$
6 : X = CO_2Me ; R = $NHCOCF_3$
7 : X = CO_2Me ; R = CO_2Me
8 : X = $CO_2{}^tBu$; R = H
9 : X = COMe ; R = H

scheme 1

alkylations using dimethyl malonate and its derivatives as a nucleophile.

The allylic alkylation reactions of 1,3-diphenyl-2-propenyl acetate (**1**) with the sodium salt of malonate ester or its derivatives were carried out in the presence of $[(\pi\text{-}C_3H_5)PdCl]_2$ and chiral diphosphine. The enantiomeric excess of the product was determined by its ^1H NMR spectra using the chiral shift reagent, $[Eu(hfc)_3]$.

The results and the reaction conditions are summarized in Table 1.[5] Using dimethyl malonate as a nucleophile high selectivity (90% ee) was obtained in the presence of (S,S)-chiraphos (entry 2).[6] Bosnich and coworkers have reported that the selectivity was 20% ee in the same reaction except that they prepared the catalyst by the method different from that of us.[7] It is noteworthy that the slight modification of the reaction conditions dramatically improved the selectivity of the reaction. The selectivity slightly dropped in the case with methylmalonate ester in place of malonate ester (entry 5),[8] and the reaction with benzylmalonate showed almost no selectivity. Consequently, the introduction of a bulky α-substituent on the nucleophile has an undesirable effect on the selectivity.

We have previously shown that acetamidomalonate ester was an excellent nucleophile in this reaction (entry 10,11).[4] However, displacement of the acetyl group by the more electron-withdrawing trifluoroacetyl group, lowered selectivity (entry 13-15). Therefore, not only steric but also electronic factors in the nucleophile seems to affect the selectivity. The selectivity was lowered by the displacement of the acetamido group by methoxycarbonyl group, too (entry 16,17). As for the ester group, substitution of the methyl group by tertiary butyl group caused no significant effect (entry 19-21). The reaction using acetylacetone in place of malonate ester was done in 90% ee with (S)-BINAP (entry 22).

The selectivity of the reaction was dependent on not only the nucleophile but also the chiral ligand employed. We have examined three chiral diphosphines, (S)-BINAP, (S,S)-chiraphos, and (S,S)-Norphos. With BINAP the selectivity was most affected by the nucleophile, ranging from 0 to 94% ee. On the other hand, the selectivity with Norphos was much less sensitive to the nucleophile, which was 74-83% ee except with benzylmalonate ester. Chiraphos was intermediate between the two.

In conclusion, this studies show that a variety of malonate ester derivatives can be successfully employed in palladium-catalyzed asymmetric allylic alkylation, and that the α-substituent of the nucleophile significantly affects the selectivity of the reaction. The method examined here has the advantage of utilizing simple and readily available chiral ligands . Further investigations are under way to extend the scope of

Table 1 Palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate and its derivatives[a]

entry	$NaCR(X)_2$		chiral ligand	time (h)	yield (%)	% ee[b]
	X	R				
1	CO_2Me	H	(S)-BINAP	44	80	30(R)
2			(S,S)-chiraphos	44	86	90(R)
3			(S,S)-Norphos	27	84	81(R)
4		CH_3	(S)-BINAP	47	33	39(R)
5			(S,S)-chiraphos	48	75	80(R)
6			(S,S)-Norphos	44	86	78(R)
7		CH_2Ph	(S)-BINAP	211	45	0
8			(S,S)-chiraphos	211	25	0
9			(S,S)-Norphos	215	88	16(R)
10[c]		$NHCOCH_3$	(S)-BINAP	120	92	94(S)
11[c]			(S,S)-chiraphos	236	98	91(S)
12[c]			(S,S)-Norphos	126	89	79(S)
13		$NHCOCF_3$	(S)-BINAP	73	94	78(S)
14			(S,S)-chiraphos	160	91	75(S)
15			(S,S)-Norphos	49	88	74(S)
16		CO_2Me	(S)-BINAP	41[d]	87	8(S)
17			(S,S)-chiraphos	127[d]	9[e]	29(S)
18			(S,S)-Norphos	16[d]	80[f]	81(S)
19	$CO_2{}^tBu$	H	(S)-BINAP	212	--[g]	26(R)
20			(S,S)-chiraphos	189	--[g]	90(R)
21			(S,S)-Norphos	393	--[g]	83(R)
22	$COCH_3$	H	(S)-BINAP	17	73	90(R)
23			(S,S)-chiraphos	18	67	63(R)
24			(S,S)-Norphos	17	67	77(R)

a The chiral ligand (1.2×10^{-2} mmol), 1,3-diphenyl-2-propenyl acetate (1mmol), and $[(\pi\text{-}C_3H_5)PdCl]_2$ (0.5×10^{-3} mmol: ligand/Pd ratio is 1.2) were dissolved in THF (4 ml) at 0° C. To a stirred suspension of sodium salt of the ester 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). The conversion was 100% unless noted otherwise. **b** Determined by ^1H NMR using $Eu(hfc)_3$. Absolute configuration in parenthesis. **c** These results were already published (ref. 4). **d** Refluxed. **e** Conversion was 11%. **f** Conversion was 90%. **g** Not isolated.

this reaction in this laboratory.

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5) The structures of all the compounds investigated were confirmed by FAB mass spectrometry, ^{1}H and ^{13}C NMR, and elemental analyses or high resolution mass spectrometry. ^{1}H NMR ($CDCl_3$, 90MHz) data of **2**: 3.51 (s, 3H); 3.69 (s, 3H); 3.94 (d, 1H); 4.27 (dd, 1H); 6.38 (dd, 2H); 7.3 (m, 10H). **3**: 1.48 (s, 3H); 3.62 (s, 3H); 3.70 (s, 3H); 4.30 (d, 1H); 6.57 (ddd, 2H); 7.3 (m, 10H). **4**: 3.18 (dd, 2H); 3.45 (s, 3H); 3.63 (s, 3H); 4.27 (d, 1H); 6.54 (ddd, 2H); 7.2 (m, 5H); 7.3 (m, 10H). **6**: 3.67 (s, 3H); 3.82 (s, 3H); 4.79 (d, 1H); 6.50 (ddd, 2H); 7.3 (m, 10H); 7.45 (s, br, 1H). **7**: 3.67 (s, 9H); 4.55 (d, 1H); 6.61 (ddd, 2H); 7.2-7.5 (m, 10H). **8**: 1.22 (s, 9H); 1.41 (s, 9H); 3.73 (d, 1H); 4.15 (dd, 1H); 6.39 (dd, 2H); 7.3 (m, 10H). **9**: 1.93 (s, 3H); 2.25 (s, 3H); 4.33 (d, 2H); 6.31 (ddt, 2H); 7.3 (m, 10H).

6) Minami and coworkers have reported that the selectivity of the similar reaction was 74% ee using a chiral phosphinocarboxylic acid as chiral ligand. Okada, Y.; Minami, T.; Sasaki, Y.; Umezu, Y.; Yamaguchi, M. Tetrahedron Lett. **1990**, 31, 3905.

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