PALLADIUM-CATALYZED ALLYLATION OF α-ISOCYANOCARBOXYLATES

Yoshihiko Ito,* Masaya Sawamura, Masato Matsuoka, Yonetatsu Matsumoto, and Tamio Hayashi* Department of Synthetic Chemistry, Kyoto University, Kyoto 606, Japan

<u>Summary</u>: α -Isocyanocarboxylates underwent palladium-catalyzed allylation with allylic acetates, in which π -allylpalladium(II) intermediate was involved. The catalytic allylation of methyl α -isocyano(phenyl)acetate using an optically active ferrocenylphosphine ligand caused an asymmetric induction of up to 39% ee.

Due to the electron withdrawing nature of isocyanide group, which may be comparable with cyanide group, alkyl isocyanides undergo carbon-carbon bond formation at the α -carbon with carbon electrophiles under basic conditions. α -Isocyanocarboxylates having hydrogens at the carbon flanked with two activating groups are more easily alkylated with various carbon electrophiles, which provide a convenient synthesis of α -amino acid derivatives.¹ Herein, we wish to report that α -isocyanocarboxylates undergo the palladium-catalyzed allylation at the α -carbon with allylic acetates. The finding is noted in that α -isocyanocarboxylate is capable of reacting as a carbon nucleophile with π -allylpalladium(II) complex, just like the so-called active methylene compounds,² since the insertion reaction of isonitrile into organometallic compounds including π -allylpalladium complex has been well known.³

The palladium-catalyzed allylation of α -isocyanocarboxylates was carried out by heating a THF solution of α -isocyanocarboxylate (1) (2.0 mmol) and allylic acetate (2.6 mmol) in the presence of 5-10 mol% of tetrakis(triphenylphosphine)palladium(0) and base (2.4 mmol) such as diazabicycloundecene (DBU), K_2CO_3 and triethylamine (eq 1). Some representative results using α -isocyanopropionate are summarized in Table 1. The ratio of the regioisomeric products, α -(1-methyl-2-propenyl)- α -isocyanopropionate (2b) and α -(2-butenyl)- α -isocyanopropionate (2b') was found to be essentially the same regardless of whether one started with 2-butenyl acetate or its regioisomer, 1-methyl-2-propenyl acetate (entries 3 and 4). The results demonstrate that the allylation proceeds via (1-methyl- π -allyl)palladium complex as a common intermediate. An anomaly of the regioselectivity may be remarked. The preferential formation of the branched isomer 2b, which arose from nucleophilic attack on more substituted carbon of the (1-methyl- π -allyl)palladium intermediate, is contrasted with the regiochemistry in palladium-catalyzed allylic alkylation with the so-called active methylene compounds.²

$$\frac{Pd(PPh_3)_4}{NC} + OAc - \frac{Pd(PPh_3)_4}{Base, THF} RCOOR'$$
(1)

entry	allyl acetate	base	reaction conditions		yield <u>b</u> (%)	product <u>c</u>	
1	CH ₂ =CHCH ₂ OAc	Et ₃ N	r.t.	1 h	81	$CH_2 = CHCH_2Z$ (2a)	
2	CH2=CHCH2OAc	K ₂ CO ₃	r.t.	45 min	n 78	2a	
<u>3d</u>	MeCH=CHCH ₂ OAc	K ₂ CO ₃	r.t.	14 h	56	CH ₂ =CHCHMeZ'(2b) 2b/2b' MeCH=CHCH ₂ Z'(2b') =62/38	
<u>4</u> <u>d</u>	CH2=CHCHMeOAc	K ₂ CO ₃	r.t.	3 h	69	2b/2b'= 57/43	
5	PrCH=CHCH ₂ OAc	DBU	r.t.	6 h	79	CH ₂ =CHCHPrZ (2c) 2c/2c' PrCH=CHCH ₂ Z (2c') =16/84	
6	MeCH=CHCHMeOAc	DBU	50 °C	4 h	69	MeCH=CHCHMeZ (2d)	
7	MeCH=CHCHMeOAc	к ₂ со ₃	50 °C	2 h	59	2d	
8	OAc	DBU	50 °C	9 h	61	Z (2e)	
9		к ₂ со ₃	50 °C	14 h	61	\bigcup	

Table 1. Palladium-Catalyzed Allylation of Ethyl α-Isocyanopropionate.ª

 $\frac{a}{2}$ 5-10 mol% of Pd(PPh₃)₄ was used as catalyst. $\frac{b}{2}$ Isolated yield by distillation. $\frac{c}{2} Z = CMe(NC)COOEt$. Z' = CMe(NC)COOMe. $\frac{d}{2}$ Reaction of methyl α -isocyanopropionate.

Synthetic utilities of the allylation products thus obtained are exemplified by the following transformations (eq 2 and 3).



The stereochemistry of the present reaction was examined with optically active 1-methyl-3-phenyl-2-(<u>E</u>)-propenyl acetate (**3**)⁴ (eq 4). When (<u>S</u>)-**3** (45% ee) was treated with methyl isocyanoacetate in the presence of Pd(PPh₃)₄ (10 mol%) and anhydrous K_2CO_3 in THF at 50 °C for 8 h, a 4 : 1 mixture of regioisomeric allylation products, α -[1-methyl-3-phenyl-2-(<u>E</u>)-propenyl]- α -isocyanoacetate (**4**) and α -(1-phenyl-2-butenyl)- α -isocyanoacetate (**4'**) was produced in 50% yield. The mixture of 4 and 4' was subjected to the reductive deisocyanation⁵ with tributyltin hydride and azobis-isobutyronitrile (AIBN) (3 mol%) to give a mixture of 5 and 5' in 63% yield. The major isomer 5 separated was determined to be an (\underline{R}) isomer of 12% ee ($[\alpha]_D^{20}$ -7.4° (\underline{c} 1.4, CCl₄)).⁴ It follows that the palladium-catalyzed allylic alkylation with α -isocyanocarboxylate proceeded with stereochemistry of 27% overall retention. Higher stereospecificity of retention (73%) was observed in the reaction with palladium-dppf catalyst⁶ in place of Pd(PPh₃)₄. The retention of configuration at the allylic carbon indicates that the isocyanoacetate attacked the π -allyl carbon from the side opposite to palladium, since the stereochemistry in oxidative addition of allylic acetate to palladium(0) forming π -allylpalladium has been established to be inversion.⁷ The α -isocyanocarboxylates are classified to a category of soft nucleophiles such as malonate and acetoacetate according to the stereochemical reaction pathway.^{2,4}





Catalytic asymmetric allylation of the α -isocyanocarboxylates 7 was carried out by using optically active ferrocenylphosphine ligand 6, which contains 2-hydroxyethylamino group on the ferrocene side chain and has proved to be one of the most effective ligands for the palladium-catalyzed asymmetric allylation.⁸ The results are summarized in Table 2. Under usual reaction conditions optical yields were low (entries 4 and 6), but addition of 1 eq of zinc halide was found to improve the stereoselectivity (entries 1, 2, 3 and 5). The highest optical yield (39%) was obtained in the reaction of methyl α -isocyano(phenyl)acetate (7a) in the presence of DBU and ZnBr₂ additive.



entry	7 (R)	base	additive	reaction temp (°C)	yield <u>b</u> (%)	[α] ²⁰ <u>c</u>	% ee <u>d</u>
1	7a (Ph)	DBU	ZnBr ₂	0	55	+18.4°	39
2	7 a (Ph)	DBU	ZnC1 ₂	0	63	+18.0°	37
3	7a (Ph)	DBU	ZnC1 ₂	20	54	+17.8°	36
4	7a (Ph)	DBU		20	22		7
5	7a (Ph)	K ₂ CO ₃	ZnCl ₂	20	28	+10.5°	24
6	7 a (Ph)	K ₂ CO ₃		20	76		0
7	7b (Me)	DBU	ZnBr ₂	20	35	-1.3°	20

Table 2. Asymmetric Allylation of α -Isocyanocarboxylates 7.^a

<u>a</u> The reaction was carried out in THF for 2-3 days in the presence of 1 mol[%] of palladium catalyst prepared in situ by mixing di- μ -chlorobis(π -ally1)dipalladium and (<u>R</u>)-(<u>S</u>)-6. <u>b</u> Isolated yield by preparative TLC on silica gel. <u>c</u> (<u>c</u> 1-2, chloroform). <u>d</u> Determined by ¹H NMR using Eu(hfc)₃.

REFERENCES AND NOTES

- a) U. Schöllkopf, Angew. Chem., Int. Ed. Engl., 16, 339 (1977).
 b) Y. Ito, T. Matsuura, and T. Saegusa, Tetrahedron Lett., 26, 5781 (1985).
 c) K. Matsumoto, T. Moriya, and M. Suzuki, J. Syn. Org. Chem. Japan, 43, 764 (1985).
- 2 For reviews: a) J. Tsuji, "Organic Synthesis with Palladium Compounds," Springer-verlag, New York (1980). b) J. Tsuji, Pure Appl. Chem., 54, 197 (1982). c) B. M. Trost and T. R. Verhoeven, "Comprehensive Organometallic Chemistry," ed by G. Wilkinson, F. G. A. Stone, and E. W. Abel, Pergamon, New York (1982), Vol. 8, p 799.
- 3 a) T. Kajimoto, H. Takahashi, and J. Tsuji, J. Organometal. Chem., 23, 275 (1970). b) Y. Ito, T. Hirao, N. Ohta, and T. Saegusa, Tetrahedron Lett., 1009 (1977).
- 4 T. Hayashi, A. Yamamoto, and T. Hagihara, J. Org. Chem., 51, 723 (1986).
- 5 T. Saegusa, S. Kobayashi, Y. Ito, and N. Yasuda, J. Am. Chem. Soc., 90, 4182 (1968).
- 6 Prepared in situ by mixing di-μ-chlorobis(π-allyl)dipalladium and l,l'-bis(diphenylphosphino)ferrocene (dppf).
- 7 T. Hayashi, T. Hagihara, M. Konishi, and M. Kumada, J. Am. Chem. Soc., 105, 7767 (1983).
- 8 a) T. Hayashi and M. Kumada, Acc. Chem. Res., 15, 395 (1982). b) T. Hayashi, A. Yamamoto, T. Hagihara, and Y. Ito, Tetrahedron Lett., 27, 191 (1986). c) T. Hayashi, "Organic Synthesis: an interdisciplinary challenge," ed by J. Streith, H. Prinzbach, and G. Schill, Blackwell Scientific Pub., (1985), p 35.

(Received in Japan 4 July 1987)