Tetrahedron Letters, Vol.31, No.25, pp 3623-3626, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

PALLADIUM-CATALYZED ASYMMETRIC ALLYLATIONS OF CHIRAL ENAMINES BEARING PHOSPHINE FUNCTIONALITY. EFFECTS OF ANIONIC COUNTERPARTS OF ALLYLATING REAGENTS ON ASYMMETRIC INDUCTION

Kunio Hiroi* and Jun Abe

Department of Synthetic Organic Chemistry, Tohoku College of Pharmacy, 4-4-1 Komatsushima, Aoba-ku, Sendai, Miyagi 981, Japan

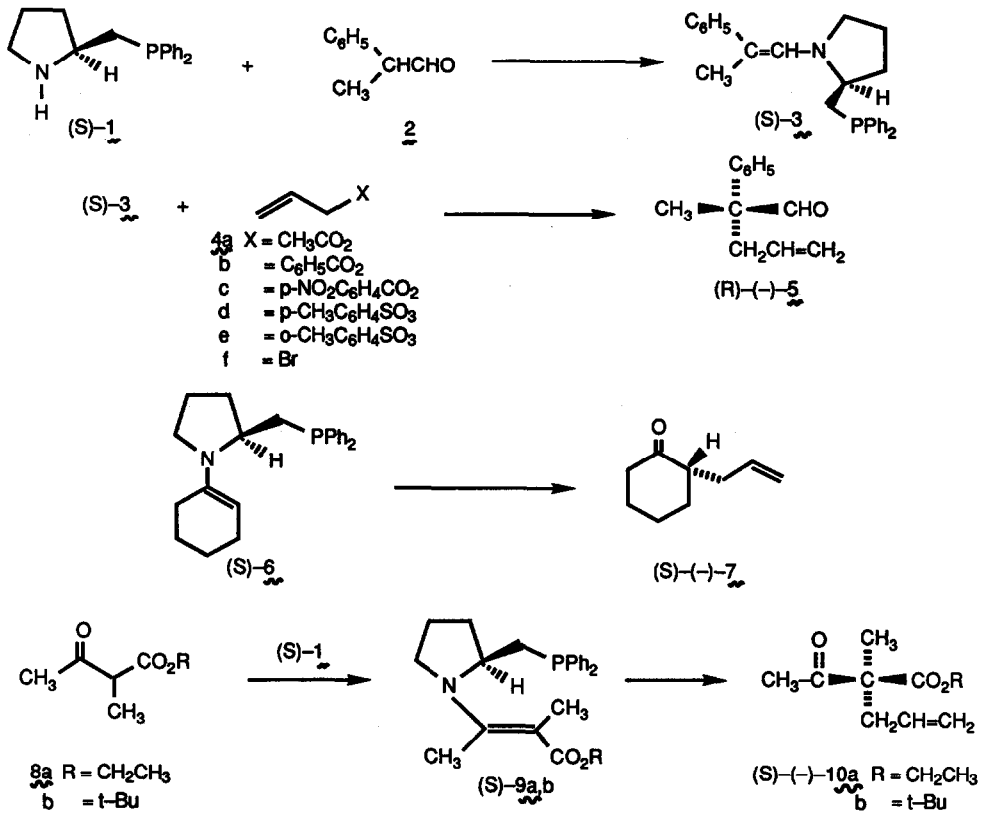
Abstract: Palladium-catalyzed asymmetric allylations of chiral enamines bearing a phosphine group were attempted using various allylating reagents to produce optically active α-allyl carbonyl compounds. The great effects of the anionic counterparts of the allylating reagents on asymmetric induction were observed.

We have explored a new method for asymmetric α-allylations of carbonyl compounds via π-allylpalladium complexes[1] of chiral enamines or imines derived from (S)-proline[2] and other (S)-α-amino acid allyl esters,[3] and revealed the mechanism of the asymmetric induction. We have further continued the investigation of the palladium-catalyzed asymmetric allylations via chiral enamines with various kinds of chiral auxiliaries.

We wish to communicate herein asymmetric allylations of chiral enamines containing a phosphorus group, which functions as a chiral phosphine ligand[4] in the palladium-catalyzed reactions and to demonstrate a great effect of anionic counterparts of allylating reagents on the asymmetric induction.

Chiral enamine (S)-3 was prepared by azeotropic dehydration of (S)-2-(diphenylphosphinomethyl)pyrrolidine (1)[5] with 2-phenylpropionaldehyde (2) in refluxing benzene for 4 h using a Dean-Stark apparatus. Reaction of the chiral enamine (S)-3 with allyl acetate (4a) (2.0 equiv.) was carried out in tetrahydrofuran (THF) at room temperature or 66 °C for 19 or 45 h in the presence of tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$], followed by hydrolysis of the allylated enamine with 10% aqueous HCl-benzene (at 80 °C for 1 h), giving (R)-(-)-2-methyl-2-phenyl-4-pentenylaldehyde (5). This reaction provided (R)-5 of the same absolute configuration as that from (S)-proline allyl ester enamines, whereas (S)-proline methyl or ethyl ester enamines produced (S)-5 upon treatment with allyl acetate under the palladium-catalyzed conditions.[2b]

In order to improve the chemical and optical yields of these allylations, stereochemical studies on these asymmetric syntheses have further been attempted employing other various allylating reagents such as allyl benzoate (4b), p-nitrobenzoate(4c), and p- or o-toluenesulfonate(4d) or (4e), and allyl bromide(4f). The results are summarized in Table I. Consequently, as shown in the Table I, a great steric effect of the anionic counterparts of the allylating reagents on asymmetric induction are observed: the optical yields



were increasing with the steric bulkiness of the anionic counterparts (X) in 4a-f. However, not as expected, the highest optical yield was represented on the reaction with allyl bromide. This means that the steric requirement by the bromine atom would be crucial in this system and advantageous for the asymmetric allylation.

This method was applicable to chiral keto-enamines. The chiral enamine (S)-6, prepared from (S)-1 and cyclohexanone, was reacted with 4 in the presence of $Pd(PPh_3)_4$ (0.2 equiv.) in refluxing THF for 19 h, followed by hydrolysis with AcONa-AcOH-H_2O-benzene (at 80 °C for 1 h), giving (S)-2-allylcyclohexanone (7).[6] The rather high optical yields were observed in the reactions with 4d and 4f, as shown in Table II.

The chiral enamine (S)-9a,b, derived from (S)-1 and 8a,b, was reacted with 4 under the same conditions as described above to give (S)-10a,b in the optical yields as listed in Table II. The highest optical yield (84%) of (S)-10b was observed when (S)-9b was reacted with 4d in refluxing THF.

The stereochemistry of these reactions was rationalized as follows: The π-allylpalladium complexes chelated with the phosphine ligands of the chiral enamines were formed and then the intramolecular allylations occurred via the intermediary complexes.The geometrical isomers 12 of the enamines (S)-3 and -9 are preferred to other isomers 11 because of the steric hindrance between the amino part and the large substituents (R^2) in 11. The conformers 13 seem to

Table I. The palladium-catalyzed Asymmetric Allylations of (S)-3

4	Reaction conditions for allylation[a] Reaction temp.(°C)	Reaction time(h)	Yield(%)[b]	Product (R)-5 $[\alpha]_D$ (MeOH)	e.e.(%)[c]
4a	r.t.	45	80	-18.8°	48
4a	66	19	86	-6.2°	16
4b	r.t.	45	78	-21.6°	57
4b	66	19	83	-11.7°	31
4c	r.t.	45	83	-27.0°	71
4c	66	19	82	-13.6°	36
4d	r.t.	45	77	-30.0°	79
4d	66	19	77	-17.8°	47
4e	r.t.	45	80	-32.0°	84
4f	r.t.	45	77	-33.3°	88
4f	66	19	90	-8.0°	21

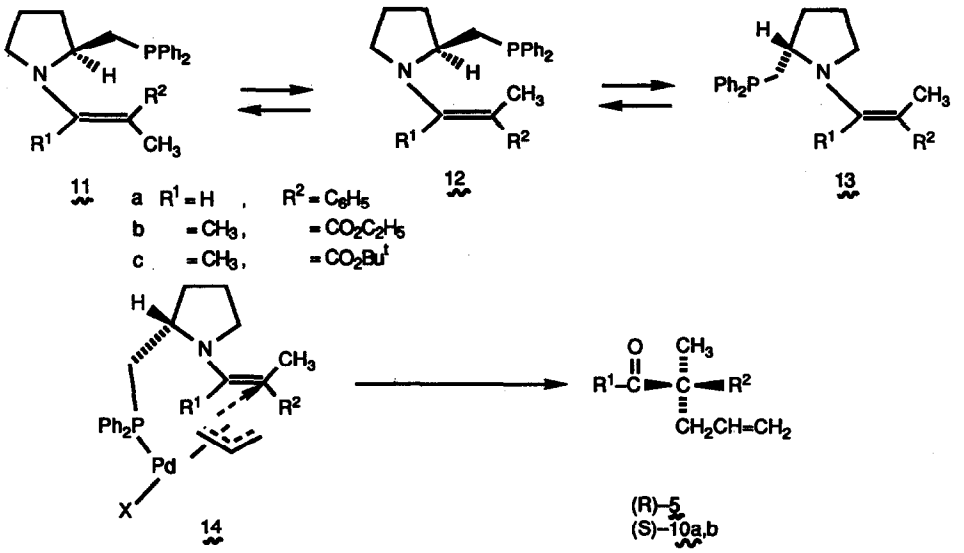
a) The reactions of (S)-3 with 4a-f were carried out in THF in the presence of $Pd(PPh_3)_4$ (0.2 equiv.) followed by hydrolysis with aqueous HCl.
b) The corrected yields based on the recovered starting material are listed.
c) The enantiomeric excess (e.e.%) was determined on the basis of the optical rotation of optically pure (R)-5 ($[\alpha]_D$-38.0°(MeOH)).

be more preferrable to 12 by the steric reason between the diphenylphosphinomethyl and the methyl group in 12. Therefore the most preferrable conformers 13 formed the π-allylpalladium complexes 14 chelated with the phosphine group and the counterparts (X), and the subsequent allylations occurred intramolecularly via the palladium complexes from the bottom side as depicted in 14, providing (R)-5 or (S)-10a,b. The steric effect by the anionic counterparts (X), presumably bonded to the palladium catalyst, would be realized at this stage. These stereochemical results were rationalized by the mechanistic pathway through the π-allylpalladium complexes similar to that of the (S)-proline allyl ester enamines.[2b] The mechanism of the asymmetric induction in cyclohexanone enamine (S)-6 was explained by the same reason as that of (S)-proline allyl ester-cyclohexanone enamine.[2a]

Table II. The Palladium-catalyzed Asymmetric Allylations of (S)-6 and -9[a]

Enamines	4	Product	Yield(%)[b]	Product $[\alpha]_D$(MeOH or $CHCl_3$)	e.e.(%)[c]
(S)-6	4a	(S)-7	57	-4.2°	27
(S)-6	4b	(S)-7	63	-4.4°	28
(S)-6	4c	(S)-7	50	-7.3°	46
(S)-6	4d	(S)-7	57	-10.3°	65
(S)-6	4f	(S)-7	55	-9.6°	61
(S)-9a	4a	(S)-10a	77	-11.0°	37
(S)-9b	4a	(S)-10b	85	-17.4°	77
(S)-9b	4b	(S)-10b	84	-14.1°	62
(S)-9b	4c	(S)-10b	84	-15.2°	67
(S)-9b	4d	(S)-10b	89	-19.0°	84
(S)-9b	4f	(S)-10b	83	-17.8°	78

a) The reactions of(S)-6 or -9a,b with 4 were carried out in refluxing THF for 19h in the presence of $Pd(PPh_3)_4$ (0.2 equiv.) followed by hydrolysis with aqueous acetic acid. b) The corrected yields based on the recovered starting materials are listed. c) The enantiomeric excess (e.e.%) was determined on the basis of the optical rotations of optically pure (S)-7 ($[\alpha]_D$-15.8°(MeOH)),[6] (S)-10a ($[\alpha]_D$-29.7°($CHCl_3$)),[7] and (S)-10b ($[\alpha]_D$ -22.7°($CHCl_3$)).[8]



Thus, this method provides the different stereochemical results, compared with those by the previous method via chiral enamines.[9] Therefore we can control the stereochemistry of the products by selecting the amino parts in chiral enamines. Accordingly, this method is useful for asymmetric α-allylation of carbonyl compounds and is also advantageous for organic synthesis, because the chiral auxiliary amine was recyclable as the starting chiral source by the efficient recovery. Furthermore, much attention should be paid to the fact that the anionic counterparts of allylating reagents provided a great effect on the asymmetric induction in these palladium-catalyzed reactions. This is the first example that demonstrated the important participation of anionic counterparts of allylating reagents in palladium-catalyzed asymmetric allylations.

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(Received in Japan 2 April 1990)